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The opinion in support of the decision being entered today is not binding precedent of the Board.

Paper ~~194~~

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

ROBERT C. ROSE, WILLIAM BONNEZ
and RICHARD C. REICHMAN,

Junior Party,
(Application 08/207,309)

v.

DOUGLAS R. LOWY, JOHN T. SCHILLER
and REINHARD KIRNBAUER,

Senior Party,
(Application 08/484,181)

Patent Interference **104,771** (NAGUMO)

DOUGLAS R. LOWY, JOHN T. SCHILLER
and REINHARD KIRNBAUER,

Junior Party,
(Application 08/484,181)

v.

C. RICHARD SCHLEGEL and A. BENNETT JENSON,

Senior Party
(Application 08/216,506)

Patent Interference **104,774** (NAGUMO)

DOUGLAS R. **LOWY**,
JOHN T. SCHILLER and REINHARD KIRNBAUER,

Junior Party,
(Application 08/484,181)

v.

IAN **FRAZER** and JIAN ZHOU,

Senior Party.
(Application 08/185,928)

Patent Interference **104,775** (NAGUMO)

Before: McKELVEY, Senior Administrative Patent Judge, LANE, TIERNEY, MOORE, and NAGUMO, Administrative Patent Judges.

MOORE, Administrative Patent Judge.

DECISION – LOWY PRIORITY DATE – BD.R. 125(a)

I. INTRODUCTION

A. **Initial Observations**

The subject matter involved in six related, but separate, Interferences 104,771 through 104,776 involves complicated biotechnology. At the outset of each interferences, the parties were advised that it would be helpful if presentations could be made using "plain English" (Paper 3). Instead, counsel for the parties have all elected to present their respective cases (both testimony and briefs) in large measure using "biotechese". We have not been able to find that any attempt was made by the

parties to present a useful glossary of terms referenced directly in the briefs. We have also not been able to find any attempt to have a witness explain the technology in more basic terms. We have not been able to find in a brief a "plain English" explanation of the subject matter involved. In short, there was no attempt to educate the board in simple terms on the technology involved. We do not know why the parties basically chose to ignore Paper 3.

If the kind of exposition we are asking for were easy to write, we probably would not need to ask parties to read and comply with ¶ 43 ("Reliance on scientific tests and data") of the Standing Order (Paper 2). The study and practical applications of complex subjects leads, necessarily, to sophisticated, technical concepts, which tend to be expressed in sophisticated, technical language. Concepts that have been reduced to things that are "patentable subject matter," however, can usually be explained to an audience in terms that explain the concepts while avoiding the technical jargon. Such explanations are not "dumbing down" the subject matter. The lack of a plain English technical background has made the case difficult to decide. Examples follow.

Rose

The Rose claims require that L1 protein in virus-like particles be recognized by sera obtained from (human) patients exposed to certain viruses. What, exactly, are "sera"? What is in them as a result of exposure to a virus and what else might be present? What tests are done to see if the L1 protein is "recognized"? What does the recognition imply about the shape of the L1 protein, and why?

Lowy

The Lowy claims call for capsids or virus-like particles capable of inducing high-titer neutralizing antibodies. What is a neutralizing antibody? How are titers measured in the laboratory, and when is a titer a "high titer"? How does one determine that an antibody is neutralizing?

Schlegel

The Schlegel claims call for L1 protein that "exhibits the same conformation" as the L1 protein on the surface of an intact human papillomavirus. Many of its proofs involve a certain kind of "ELISA" measurement. What is actually measured? What is the significance of what is measured?

Frazer

> Frazer, due to the nature of its case, does not offer proofs for priority based on laboratory notebooks or the outcome of particular experiments. But its case requires that we understand the descriptions in its specifications and printed publications of the results of recombinant DNA technology, the production of proteins, and the assembly of proteins into particles resembling viruses.

A number of questions arose as we considered the laboratory experiments, measurements, and technical arguments on which the parties relied to prove conception or actual reduction to practice. How was the experiment done? What was actually measured? How reliable is the measurement? What controls ought to be done? Why? What is the level of the signal compared to the noise? How reproducible is the assay? How do the measurements relate to the conclusions the moving party would have us draw from its experiments? Why is the movant's proposed explanation the most likely explanation? What else could have led to the same result? These are the types of questions that ¶ 43 of the Standing Order indicates should be explained. We often found ourselves asking these questions as we sought to

resolve the issue of priority in this interference. Seldom, however, could we find a simple, straightforward explanation in the briefing or in the record. Perhaps the parties assumed--erroneously--that we knew all about the experiments. What is absolutely plain is that all parties simply did not comply with the provisions of ¶ 43 of the Standing Order (Paper 2, page 30).

As a result, we have spent a good amount of time searching the record for the teachings we requested in ¶ 43 of the Standing Order. We have spent additional time assuring ourselves that our understanding, expressed in plain English, is accurate. We have attempted to summarize the major features of the involved technology for the general reader in Appendix I, which is attached to this decision. We remain somewhat nonplused that the parties would provide so little guidance to the technical foundations of their cases.

As indicated during oral argument during the priority phase, we had hoped to have final decisions entered in these six interference on or before 15 August 2005. Instead, final decisions are being entered about a month later. The "delay" in entering final decisions in large measure can be attributed to the lack of a "technical education" in "plain English" by each of the parties.

In future cases, our hope is that parties take the time to educate the board in "plain English" on the nature of the technology involved in an interference.

B. **Background**

This is a decision on Lowy's priority case.

Oral arguments in related interferences 104,771 through 104,776 were held on 30 June 2005 before a court reporter. Michael Goldman, Esq., argued for Rose. Brenton Babcock, Esq., and Nancy Vensko, Esq., argued for Lowy. Beth Burrous, Esq., argued for Frazer. Elliot Olstein, Esq., argued for Schlegel.

For the reasons set out herein, we hold that Lowy has not proven a conception, nor diligence, nor an actual reduction to practice prior to the filing date of its benefit application 07/941,371, filed September 3, 1992. Thus, the earliest priority date to which Lowy is entitled is September 3, 1992.

Initial Findings of Fact

The record of these interferences supports the following findings of fact by at least a preponderance of the evidence.

For Interference 104,771

F771-1. This interference was redeclared (Paper 128) with the following Count:

A composition of matter according to any of claims 42, 43 or 65 of Rose or a method according to any of claims 44, 56 or 71 of Rose,

or

A composition of matter according to either of claims 48[1] or 49 of Lowy.

F771-2. Lowy's claim 49 reads:

Isolated papillomavirus-like particles comprising an L1 polypeptide which contains at least one conformational epitope and is capable of inducing high-titer neutralizing antibody, produced by the method comprising: permitting a genetic construct, comprising a papillomavirus L1 gene, to direct recombinant expression and self-assembly of papillomavirus-like particles comprising the L1 polypeptide in a transformed eukaryotic host cell; and isolating said self-assembled particles.

F771-3. Lowy's involved application, 08/484,181 (Lowy '181), was filed on 7 June 1995. The Lowy '181 application was filed as a division of application 07/941,371 (Lowy '371), which was filed on 3 September 1992. In the decision on motions, Lowy has been accorded the benefit for priority of the Lowy '371 application.

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[1] Claim 48 has been determined to be unpatentable to Lowy in interference 104775. Whether or not claim 48 has been determined to be unpatentable in some other interference is irrelevant to the considerations in this interference. In any event, our analysis focuses on claim 49, and the patentability of claim 48 is of no consequence to the analysis herein.

F771-4. Rose's involved 08/207,309 (Rose '309) application was filed 7 March 1994. The Rose '309 application was filed as a continuation-in-part of application 08/028,517 (Rose '517), which was filed on 9 March 1993. Rose has been accorded benefit for priority of the Rose '517 application.

F771-5. Lowy is the senior party.

For Interference 104,774

F774-1. As a result of the decision on preliminary motions (Paper 102), this interference was redeclared (Paper 107) with the following count:

> A composition of matter according to either of claims 48 or 49 of Lowy,
>
> or
>
> A composition of matter according to any of claims 1, 12, 50 or 64 of Schlegel or a method according to any of claims 19, 53 or 55 of Schlegel.

('774 Interference, Paper 107 at 2.)

F774-2. Lowy's claim 49 reads as in F771-2.

F774-3. Lowy's involved application, 08/484,181 (Lowy '181), was filed on 7 June 1995. The Lowy '181 application was filed as a division of application 07/941,371 (Lowy '371), which itself was filed on 3 September 1992. Lowy has been accorded the benefit for priority of the Lowy '371 application.

F774-4. Schlegel's involved application, 08/216,506 (Schlegel '506) was filed 22 March 1994. The Schlegel '506 application was filed as a continuation of the 07/903,109 (Schlegel '109) application, which itself was filed on 25 June 1992. Schlegel was accorded the benefit for priority of the Schlegel '109 application.

F774-5. Lowy is the junior party.

For Interference 104,775

F775-1. The Count has been redeclared as follows (Paper 150):

> A composition of matter according to claim 49 of Lowy,
>
> or
>
> a composition of matter according to claim 67 of Frazer or a method according to any of claims 65, 89 or 97 of Frazer.

F775-2. Lowy's claim 49 reads as in F771-2.

F775-3. Lowy's involved application, 08/484,181 (Lowy '181), was filed 7 June 1995. The Lowy '181 application was filed as a division of application 07/941,371 (Lowy '371), which was itself filed on 3 September 1992. Lowy has been accorded the benefit for priority of the Lowy '371 application.

F775-4 Frazer's involved 08/185,928 (Frazer '928) application was filed on 19 January 1994 as the national stage (35 U.S.C. § 371) of PCT application PCT/AU92/00364 (PCT), filed 20 July 1992, which in turn is based on Australian application PK 7322 (Australian), which was filed on 19 July 1991. Frazer has been accorded the benefit for priority of the PCT application only. Frazer has been denied the benefit for priority of the Australian application.

F775-5. Lowy is the junior party.

II. The Issues

A. **Summary By Interference**

For Interference 104,771

Lowy is the senior party. Lowy need not put on a priority case to prevail, unless Rose establishes prior conception followed by reasonable diligence until a reduction to practice from a time prior to Lowy's constructive reduction to practice of September 3, 1992. As set forth in the opinion authored by Judge Lane, filed concurrently herewith, Rose has not done so. Accordingly, we need not analyze Lowy's proofs in the '771 Interference, and Rose does not prevail in the '771 interference.

For Interference 104,774

Lowy is the junior party and has the burden of proving it was the prior inventor. As Lowy has not done so, Lowy does not prevail in the '774 interference.

For Interference 104,775

Lowy is the junior party and has the burden of proving it was the prior inventor. As Lowy has not done so, Lowy does not prevail in the '775 interference.

B. Lowy's Position

Lowy takes the position that it should be granted priority over Schlegel and Frazer because: (i) Lowy's alleged corroborated actual reduction to practice by March 26, 1992 predates Schlegel's constructive reduction to practice of June 25, 1992 and Frazer's constructive reduction to practice of July 20, 1992; and, alternatively, that (ii) Lowy conceived the invention on December 19, 1991. ('774 Interference Paper 123, page 1)('775 Interference Paper 167, page 1).

C. Lowy's Burden

To obtain the benefit of its alleged date of actual reduction to practice, Lowy has the burden of proving its conception and its actual reduction to practice by a preponderance of the evidence (37 CFR §41.207(a)(2); see also former 37 CFR §1.657(b))).

D. Schlegel's Position

Schlegel, on the other hand, asserts that Lowy cannot establish an earlier conception or actual reduction to practice because it never demonstrated isolated virus-like particles (VLPs) as required by Lowy claim 49, towards which Lowy directs its proofs. ('774 Interference, Paper 127, page 7).

E. Frazer's Position

Frazer also asserts that Lowy failed to prove conception and actual reduction to practice. ('775 Interference, Paper 181, page 1). Frazer urges that Lowy's VLPs "were not isolated" and thus "they did not meet all the limitations of the Count" ('775 Interference, Paper 181, page 4).

F. Summary of Opinion

We hold that Lowy has failed to prove, by a preponderance of the evidence, that Lowy conceived or actually reduced the invention of the count to practice at any time prior to Lowy's filing date at least insofar as Lowy has failed to prove its VLPs were "isolated."

Lowy had the burden of proving, within the context Lowy claim 49, an alternative of the count, what the term "isolated" and the step of "isolating" would have meant to one of ordinary skill in the art at the time the application was filed, and that Lowy's proofs fall within the count. Lowy has:

(i) failed to direct us to any definition in its specification (indeed, has overlooked the instances of usage of the terms in its own specification);

(ii) failed to provide us with an adequate definition of these terms, from any source, let alone a qualified expert;

(iii) provided as late-submitted proofs of the meaning of the terms "isolated" and "isolating" (i.e., in its reply briefs) several articles reciting processes which have not been shown to be in the context of Lowy claim 49 and which fail to identify the terms or provide a definition within the context of the claim; and

(iv) attempted to define the terms by inference from a previous Board decision or oblique references to the level of purification necessary for isolation without relating its arguments to the context of Lowy claim 49.

We do not credit any of these indirect attempts to define the reasonable breadth of the terms of claim 49. Instead, we look to, and credit:

(i) the language of claim 49 and how the terms "isolated" and "isolating" are used in context of the claim as a whole;

(ii) the usage of the terms "isolated" and "isolating" in the specification;

(iii) the prosecution history of the application involving the addition of the terms to claim 49;

(iv) the common definition of the terms as gleaned from three dictionaries; and

(v) admissions from Lowy's own witnesses which support the broadest reasonable definition of the terms in the context of Lowy's claim 49.

"Isolating" includes physically separating the VLPs from the producing cells, for the claim's functional requirement of providing "isolated" VLPs capable of raising high-titer neutralizing antibodies.

As a consequence, we hold that Lowy has not shown that it "isolated" its VLPs within the meaning of the term as it is used in the count at any time, and Lowy's earliest date of priority is its constructive reduction to practice of September 3, 1992.

Our detailed reasoning follows.

III. The Pertinent Law

A. First to Reduce to Practice

While simplified, a single sentence accurately sums up all of the complexities of interference law in this particular circumstance. The party "A" who reduced to practice first is adjudged the first inventor, unless the other party "B" conceived the invention first and was diligent from prior to A's conception

until B's later reduction to practice. See Hitzeman v. Rutter, 243 F.3d 1345, 1353, 58 USPQ2d 1161, 1166 (Fed. Cir. 2001) ("priority of invention is awarded to the first party to reduce an invention to practice unless the other party can show that it was the first to conceive of the invention and that it exercised reasonable diligence in later reducing that invention to practice"); Haskell v. Colebourne, 671 F.2d 1362, 1365, 213 USPQ 192, 194 (CCPA 1982) ("Appellants must establish that they actually reduced to practice the invention of the counts before July 17, 1972, Colebourne's actual U.S. filing date, or that they conceived the invention prior to that date and proceeded with diligence toward a reduction to practice, either actual or constructive."); Keizer v. Bradley, 270 F.2d 396, 400, 123 USPQ 215, 218 (CCPA 1959) (there is no penalty to the first inventor who diligently works to reduce it to practice).

B. Evidence

Lowy acknowledges that "[e]vidence to support either a conception or a reduction to practice of an invention must meet the highest level of scrutiny with respect to the type of evidence offered and the corroboration of that evidence" (Paper 123, page 5).

C. Requirements for Conception/Actual Reduction to Practice

In an interference proceeding, a party seeking to establish conception must prove formation, in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is thereafter to be applied in practice. Coleman v. Dines, 754 F.2d 353, 359, 224 USPQ2d 857, 862 (Fed. Cir. 1985). Conception requires both the idea of the invention's structure and possession of an operative method of making it. Oka v. Youssefyeh, 849 F.2d 581, 583, 7 USPQ2d 1169, 1171 (Fed. Cir. 1988). Accordingly, the inventor must have at least a reasonable expectation that the inventor can produce an invention of the count in order to establish a conception. Where the specific result of an unpredictable process is part of the count, conception cannot occur absent a reasonable expectation that the result of the process would occur. Hitzeman v. Rutter, 243 F.3d 1345, 1358, 58 USPQ2d 1161, 1169 (Fed. Cir. 2001).

In an interference proceeding, a party seeking to establish an actual reduction to practice must satisfy a two prong test: (1) the party constructed an embodiment or performed a process that met every element of the interference count, and (2) the embodiment or process operated for its intended purpose. Eaton v. Evans, 204 F.3d 1094, 1097, 53 USPQ2d 1696, 1698 (Fed. Cir. 2000).

IV. Lowy's Priority Case

Additional Findings of Fact

F774-6; F775-6. According to Dr. Howley, testifying on behalf of Lowy, a neutralization assay is a test which determines whether the VLP has the ability to induce high-titer neutralizing antibodies. (LX 3385, Declaration of Dr. Howley, paragraph 71).

Discussion

A. Lowy's Required Proofs

Lowy focuses its conception and actual reduction to practice discussion on claim 49 ('774 Interference, Paper 123, pages 14-15; '775 Interference, Paper 167, pages 14-15), which defines an alternative of the count, and is as follows (using Lowy's labels for the limitations of the claim):

> [A] Isolated papillomavirus-like particles comprising an L1 polypeptide
>
> [B] which contains at least one conformational epitope
>
> [C] and is capable of inducing high-titer neutralizing antibody,
>
> [D] produced by the method comprising: permitting a genetic construct, comprising a papillomavirus L1 gene,
>
> [E] to direct recombinant expression and self-assembly of papillomavirus-like particles comprising the L1 polypeptide in a transformed eukaryotic host cell;
>
> [F] and isolating said self-assembled particles.

Lowy's initial conception is said to have occurred on December 19, 1991 when it visualized virus-like particles (VLPs) in electron micrographs, and believed that they might contain conformational epitopes that induce high-titer antibodies. ('775 Interference, Paper 167, pages 14-16).

Lowy's actual reduction to practice is said by Lowy to have occurred on March 26, 1992. ('774 Interference, Paper 123, page 5; '775 Interference, Paper 167, page 5). It is on this date that Lowy's second neutralization assay is alleged by Lowy to have been completed ('774 Interference, Paper 123, page 3, paragraph 11; '775 Interference, Paper 167, page 3, paragraph 11).

Lowy's version of the events which define its alleged actual reduction to practice of the invention of the count is as follows.

(I) According to Lowy, on October 30, 1990, Dr. Lowy (inventor) stated to Dr. Schiller (inventor) that the key to making a papillomavirus vaccine was the formation of virus-like particles. (Lowy Declaration, LX 3381, paragraph 16).

(II) Lowy states that, by September 23, 1991, Lowy's inventors cloned a papillomavirus L1 gene into a baculovirus vector and transformed a host cell with the baculovirus insect vector. (Lowy Declaration, LX 3381, paragraph 20).

(III) Dr. Lowy states that Lowy's inventors permitted the transformed host cell culture to grow, and that by December 6, 1991, Lowy determined that the transformed host cell was producing a 55 kDa protein, about the right size for an L1 protein. (Lowy Declaration, LX 3381, paragraphs 22, 23, and 24).

(IV) On December 8, 1991 Lowy allegedly confirmed that the 55 kDa protein was an L1 protein (Lowy Declaration, LX 3381, paragraph 23), and shipped the host cells out for electron micrographic analysis on December 9, 1991. (Lowy Declaration, LX 3381, paragraph 26).

(V) On December 19, 1991 Dr. Monticello (an anatomical pathologist) allegedly sent electron micrographs back to Lowy which confirmed size, shape, amount, and location of these virus-like particles. (Lowy Declaration, LX 3381, paragraph 27).

(VI) On March 26, 1992 the results of Lowy's second neutralization assay are alleged to have successfully reduced infectivity of bovine papillomavirus (BPV) by 100% (i.e. raised high-titer neutralizing antibodies) (Lowy Declaration, LX 3381, paragraph 39).

B. Interpreting the Count

Additional Findings of Fact

F774-7; F775-7. Lowy claim 49, which defines an embodiment of the count, reads in part as follows (emphasis added):

> **Isolated papillomavirus-like particles comprising** an L1 polypeptide . . . produced by the method comprising: permitting . . . **and isolating said self-assembled particles.**

F774-8; F775-8. Lowy's specification states that viruses are characterized after being harvested from papillomas [warts] for research. (LX 3051, page 2).

F774-9; F775-9. Lowy's specification observes that bovine papillomaviruses (BPVs) are preferred for research because of the "large amounts of infectious virus particles can be isolated from bovine papillomavirus (BPV) warts" (LX 3051, page 2, lines 12-19).

F774-10; F775-10. Lowy's specification states that its process includes a step of "isolating capsomer structures or capsids, comprising L1 capsid protein from the cell" (LX 3051, page 5, line 30 - page 6, line 5).

F774-11; F775-11. Lowy inventor Schiller testified that isolation meant the following to him:

> Q But would it be fair to say that when you isolate something, you separate it from the other things with which that thing that you want to be isolated is normally associated with?
>
> A Yeah, I would -- I guess I would agree with that, yeah. [LX 3475, p. 156-157]

F774-12; F775-12. In discussing a process for isolating particles in its specification, Lowy characterized the process as follows:

> . . . partially purified particles isolated by differential centrifugation and ammonium sulfate precipitation. [LX 3051, sentence spanning pages 13 and 14].

F774-13; F775-13. Webster's New Collegiate Dictionary (1979) discloses three following potential definitions at page 608:

> [1]**iso-late** [pronunciations omitted] *vt* **-lated; -lating** [back-formation from *isolated* set apart, fr. F isole, fr. It *isolato*, fr. *Isola* island, fr. L *insula*] **1**: to set apart from others; *also*: QUARANTINE **2**: to select from among others; *esp*: to separate from another substance so as to obtain pure or in a free state **3**: INSULATE. (Page copy attached as appendix A hereto).

F774-14; F775-14. The McGraw Hill Dictionary of Scientific and Technical Terms (2nd Edition, 1978) defines isolation at pages 849-850 as follows, in pertinent part:

> **isolation** [CHEM] Separation of a pure chemical substance from a compound or mixture; as in distillation, precipitation, or absorption. [MED] Separation of an individual with a communicable disease from other, healthy individuals. [MICROBIO] Separation of an individual or strain from a natural, mixed population. (Page copy attached as Appendix B hereto).

F774-15; F775-15. Hawley's Condensed Chemical Dictionary (14th Edition, 2001) defines isolation on page 626 as follows:

> **isolation**. Identification and separation of a pure substance that is present in trace amounts in a complex mixture. A famous instance of this was the isolation of polonium (1898) and radium (1912) from pitcheblende by the Curies by coprecipitation techniques followed by repeated fractional crystallization. (Page copy attached as Appendix C hereto).

F774-16; F775-16. Dr. Howley, Lowy's expert, testified that:

> Q When you talk about the term isolated, what does that term mean to you if you were to talk about an isolated protein? What does isolated mean?
>
> A It would be I think comparable to purified. (LX 3476, answer spanning pages 209-210).

F774-17; F775-17. "isolating said self assembled particles," to one of ordinary skill in the art at the time Lowy's application was filed, would have included physically

separating the VLPs from the producing cells, for the claim's functional purpose of providing "isolated" VLPs capable of raising high-titer antibodies(LX 3051, page 6, line 30 - page 7, line 5).

F774-18; F775-18. Dr. Monticello, Lowy's witness, testified that, in analyzing the electron micrographs of the VLPs:

> 11. In comparison to the wild type baculovirus-infected cells, the cells infected with the BPV recombinant virus contained many circular structures of approximately 50 nm, which were preferentially localized in the nucleus of cells. These results indicated that self-assembly of L1 into virus-like particles had occurred, since in vivo papillomavirus virion assembly takes place in the nucleus and the diameter of the virions (spherical in shape) had been reported as 55 nm. (LX 3402)

F774-19; F775-19. Dr. Monticello testified that the VLPs in the sliced cells were located in the nucleus. (LX 3402, paragraph 12)

Discussion

As noted above, in the '774 and '775 interferences, Lowy must show ***each*** element of the count, including an "isolated" VLP capable of inducing high-titer neutralizing antibody, prepared by a step of "isolating" to establish either a conception or a reduction to practice.

We, as a consequence, need to examine the scope of the count; particularly including what is meant by "isolated" and the step of "isolating" as used in Lowy claim 49.

Interference counts are given their broadest reasonable interpretation. See Davis v. Loesch, 998 F.2d 963, 968, 27 USPQ2d 1440, 1444 (Fed. Cir. 1993). However, there are limits to the breadth of this claim interpretation. We must give weight to all claim limitations. See, e.g. In re Angstadt, 537 F.2d 498, 501, 190 USPQ 214, 217 (CCPA 1976). As a general rule, claim language carries the ordinary meaning of the words in their normal usage in the field of invention. Toro Co. v. White Consol. Indus., 199 F.3d 1295, 1299, 53 USPQ2d 1065, 1067 (Fed. Cir. 1999).

We note that in its specification and in its principal briefs on priority Lowy has provided us with no definition of the scope of the terms "isolated" and "isolating said self-assembled particles" in the context of Lowy claim 49.

Lowy's brief on priority is devoid of useful evidence or significant analysis on this point. ('774 Interference, Paper 123; '775 Interference, Paper 167).

In presenting its prima facie case for priority, Lowy simply assumes, without demonstrating, that:

> - "isolated" as used in the context of thin sectioning electron micrographs for visualization of the structures contained therein is within the scope of the count as relates to isolating VLPs from host cells ('774 Interference, Paper 123, page 16, lines 15-16, and '775 Interference, Paper 167, page 16, lines 1-3)

and

> - "isolated" as used in the context of making whole-cell lysates of insect cells, which contain the entire cell contents, is within the scope of the count as relates to isolating VLPs from host cells ('774 Interference, Paper 123, page 16, lines 19-21, and '775 Interference, Paper 167, page 19, lines 8-11).

We need to look to the claim, then the specification and prosecution history, and other sources as necessary to see if a definition of the term "isolated" or the step of "isolating" is provided or implied.

As recently stated by our reviewing court in Phillips v. AWH Corp., 415 F.3d 1303, 1313, 75 USPQ2d 1321, 1326 (Fed. Cir. 2005):

> The inquiry into how a person of ordinary skill in the art understands a claim term provides an objective baseline from which to begin claim interpretation. See Innova, [381 F.3d 1111, 1116, 72 USPQ2d 1001, 1004, Fed. Cir 2004]. That starting point is based on the well-settled understanding that inventors are typically persons skilled in the field of the invention and that patents are addressed to and intended to be read by others of skill in the pertinent art. See Verve, LLC v. Crane Cams, Inc., 311 F.3d 1116, 1119 [65 USPQ2d 1051] (Fed. Cir. 2002) (patent documents are meant to be "a concise statement for persons in the field"); In re Nelson, 280 F.2d 172, 181 [126 USPQ 242] (CCPA 1960) ("The descriptions in patents are not addressed to the public generally, to lawyers or to judges, but, as section 112 says, to those skilled in the art to which the invention pertains or with which it is most nearly connected.").
>
> Importantly, the person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification.

We start with the plain language of the claim. The claimed particles are "**[i]solated papillomavirus-like particles** ... produced by the method comprising: permitting a genetic construct . . . to direct recombinant expression and self-assembly of papillomavirus-like particles . . . **and isolating said self-assembled particles.**" (Lowy claim 49).

"Proper claim construction . . . demands interpretation of the entire claim in context, not a single element in isolation." Hockerson-Halberstadt, Inc. v. Converse Inc., 183 F.3d 1369, 1374, 51 USPQ2d 1518, 1522 (Fed. Cir. 1999); ACTV, Inc. v. Walt Disney Co., 346 F.3d 1082, 1088-90, 68 USPQ2d 1516, 1521-23 (Fed. Cir. 2003) ("While certain terms may be at the center of the claim construction debate, the context of the surrounding words of the claim also must be considered . . . ."); Brookhill-Wilk 1, LLC v. Intuitive Surgical, Inc., 334 F.3d 1294, 1299, 67 USPQ2d 1132, 1136 (Fed. Cir. 2003) (same).

In reading Lowy claim 49, we conclude that the claim as a whole is directed to papillomavirus like particles that have been produced using recombinant technology in a host cell and then isolating the particles. The isolated papillomavirus-like particles must be capable of inducing neutralizing antibodies.

The preamble of the claim requires "isolated" particles. The claim requires a step of "isolating said self-assembled particles" after the particles have been formed in the cell.

The step of "isolating" the particles is more than simply identification. The claim itself implies physical separation of the produced virus-like particles (VLPs) from the producing cells, for the claim's functional purpose of providing "isolated" VLPs capable of raising high-titer antibodies.

This interpretation is supported by the specification. In the specification, Lowy uses the term "isolating" in the same context as in claim 49. For example, when discussing isolation of a capsid (a VLP), it is in terms of isolating the capsid *from the cell* (i.e. removing, by separating):

> According to another aspect of the invention there is provided a method for producing a recombinant papillomavirus L1 or L1 and L2 capsid protein, assembled into a capsomer structure, or a capsid structure, comprising the steps of cloning a papillomavirus gene, coding for an L1 conformational capsid protein sequence, into a transfer vector in which the open reading frame of said gene is under the control of the vector promoter; transferring the recombinant vector into a host cell, wherein the cloned papillomavirus gene expresses the papillomavirus capsid protein; **and isolating capsomer structures or capsids, comprising L1 capsid protein <u>from the cell</u>** (LX 3051, page 5, line 30 - page 6, line 5)(emphasis added).

In preparing the particles for testing, Lowy's specification again uses the term "isolating," in the context of isolating VLPs, to mean at least partial separation:

> Two types of preparations were tested: whole cell extracts of L1 recombinant or wild type infected Sf-9 cells and **partially purified particles isolated by differential centrifugation and ammonium sulfate precipitation.** [LX 3051, sentence spanning pages 13 and 14][emphasis added].

The term "isolated" as used in this portion of the specification, in the context of isolating the virus for purposes of raising antibodies (eliciting an immune response) persuades us that "isolation," as used in claim 49, includes some form of separation of the virus by separation from the host cells.

We also observe Lowy added the "step" of "isolating" (LX 3590, page 2)(Responsive Amendment in Lowy '181, dated October 30, 1996) when suggesting a claim for this interference. To obviate a potential rejection over a naturally occurring virion by a step of isolation also implies some form of separation to remove the VLPs from the host cell, i.e. its natural environment. Accordingly, Lowy's prosecution history supports the interpretation of "isolating" the self assembled particles as requiring some separation from the host cell which grew the particles.

We have consulted several dictionaries in search of a standard meaning. Beginning with a general dictionary, we observe the definition of isolate requires setting apart.[2] A standard microbiology definition requires separation.[3] A chemical definition requires identification and separation.[4] Separation from the host cell is the most reasonable broadest meaning of the term "isolate" within the context of claim 49 and its supporting specification.

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[2] Webster's New Collegiate Dictionary (1979) discloses three potential definitions at page 608, of which only one is a verb:

[1] **iso-late** ... **1**: to set apart from others; *also*: QUARANTINE **2**: to select from among others; *esp*: to separate from another substance so as to obtain pure or in a free state **3**: INSULATE. [Page copy attached as appendix A hereto].

[3] The McGraw Hill Dictionary of Scientific and Technical Terms (2nd Edition, 1978) defines isolation at pages 849-850 as follows, in pertinent part:

isolation [CHEM] Separation of a pure chemical substance from a compound or mixture; as in distillation, precipitation, or absorption. [MED] Separation of an individual with a communicable disease from other, healthy individuals. [MICROBIO] Separation of an individual or strain from a natural, mixed population. [Page copy attached as Appendix B hereto].

[4] Hawleys Condensed Chemical Dictionary (14th Edition, 2001) defines isolation on page 626 as follows:

isolation. Identification and separation of a pure substance that is present in trace amounts in a complex mixture. A famous instance of this was the isolation of polonium (1898) and radium (1912) from pitcheblende by the Curies by coprecipitation techniques followed by repeated fractional crystallization. (Page copy attached as Appendix C hereto).

Our interpretation is further supported by the testimony of Dr. Schiller, one of Lowy's own inventors. When questioned on the meaning of isolated, Dr. Schiller admitted "isolated" was a relative term, relative to the context of the operation the person isolating the substance needed it for. His testimony was as follows:

> Q ... if you have a starting material -- say you've got a cell with a recombinant protein in it. You could do -- you could lyse the cells and spin them down and say you knew the protein would end up in the cell pellet, so you'd have a supernatant and a pellet. Would you consider the pellet to be -- contain isolated protein?
>
> A I would probably call it enriched, if that's what -- you know, if there was more of it in there and it was readily detectable, you know. Again, and it depends upon the relative amounts of that protein versus everything else in that pellet. **If a large percentage of that pellet was specifically that protein -- for instance, if you do an ammonium sulfate precipitation and you got a lot of that protein out, then you could consider it operationally isolated, isolated well enough for you to do what you want to do. For instance, let's say with VLPs, if you wanted to look at whether you see nice, you know, beautiful VLPs, you wouldn't necessarily have to separate it from 95 percent of all other-cellular proteins. But if you want to do negative staining, you may want to have it separated from 50 percent of the proteins so you can see it and get -- especially separated from other aggregates.** Other soluble proteins may not be a problem. So, again, I'm not trying to be evasive, but it's very contextual. How you would operate - it's an operational definition. It's not an absolute definition. (LX 3475, page 155, line 2 - page 156, line 10) (emphasis added)

Dr. Schiller's testimony reveals that his understanding of isolation involves how pure the isolate has been made from an operational context. For example, according to Dr. Schiller, to identify VLPs by negative staining, one would need to isolate the VLPs down to about 50% purity vis-a-vis the other proteins. Translating this operational contextual definition to the claim indicates that "isolate the self assembled particles" is in the context of producing isolated particles which would be used to generate an immune response following their production from a recombinant virus, as grown in a host cell. Dr. Schiller's testimony supports a definition of "isolated" as requiring at least some separation to remove the VLPs from the host cell.

Finally, we observe that Lowy's expert, Dr. Howley, stated that "isolated" is more akin to "purified" in the context of an isolated protein (LX 3476, answer spanning pages 209-210).

> Q When you talk about the term isolated, what does that term mean to you if you were to talk about an isolated protein? What does isolated mean?
>
> A It would be I think comparable to purified.

While Dr. Howley's testimony is not strictly in the context of claim 49, it supports our interpretation including separation.

"Isolated," therefore, requires at least some separation of the VLPs from the producing host cells. Lowy has provided no

persuasive evidence that it separated the VLPs from the cells which were imaged in the electron micrographs, in the sense of Lowy claim 49. Lowy has also provided no persuasive evidence that the whole cell lysates which were used to immunize the rabbits contained "isolated" VLPs, in the sense of Lowy claim 49.

Lowy's Belated Expansive Definition of "Isolated"

In reply to Schlegel's and Frazer's oppositions, Lowy for the first time in its reply briefs asserts a definition of isolated. While normally we would not entertain such belated evidence or argument, we in this case discuss it as it further supports the interpretation we have given the terms "isolated" and "isolate."

Lowy's supplemental attempt to define the term fails on several fronts. First, Lowy again has failed to define the term within the scope of Lowy claim 49. What "isolated" might mean in various fields or different endeavors bears little persuasive value when the field we are interested in is defined within the context of claim 49.

For example, Lowy states that:

> Thus, at the time of Lowy's invention, those skilled in the art used the terminology "isolated" to refer to the identification of viruses using viruses which had been separated from their natural environment (e.g., dissociated from at least some of the materials with which they are associated in intact cells) but which had not been fully purified. ('774 Interference, Paper 132, page 49, lines 3-6).

Lowy has not explained why this argument is pertinent to the interpretation of the term "isolated" within the context of Lowy claim 49. Identifying infectious agents in the wild by removing them from their natural environment is not the same as isolating VLPs which have been prepared by recombinant DNA technology in a known host cell and "isolating" the VLPs, when the VLPs are intended to be used to induce neutralizing antibodies. Lowy is equating apples and oranges in this instance.

Lowy's definition of "isolated" is also an exercise in semantics. In its parenthetical in the above-quoted "definition," Lowy further expands upon its original expansive reading of the term "isolated." Lowy asserts that an example of such separation is as broad as "dissociation" from at least some of the materials with which they are associated in an intact cell. Lowy is further expanding its definition of "isolated" out of the context of claim 49.

First, "dissociated" itself can have several meanings (See Appendix D hereto). Among them are: "...to cut off (as from society) ... separate esp. from association or union with another: disconnect from association with another ... to separate into discrete units or parts: DISUNITE ... to subject to chemical dissolution ..." Lowy has provided no bounds for this term and no context in which to understand it.

Second, Lowy has not demonstrated, what, if anything, Lowy's VLPs were dissociated from.

Third, Lowy has not explained at all why "dissociation" can be equated to separation from their natural environment. Lysing cells appears to be quite different from pulling an infectious agent out from the wild by removing the virus from the index host. Lowy has again assumed a connection rather than actually proven one.

Lowy in its reply brief ('774 Interference Paper 132) attempts to buttress its multiple assumptions by asserting its expansive definition is "consistent with":

(1) the meaning of the term in the field of virology

(2) the Board's decision on Preliminary Motions

(3) Lowy '181's specification

(4) the Federal Circuit's interpretation of this term.

An interpretation of a term can be "consistent with" another interpretation and still not be an accurate interpretation.

What Lowy should have done was analyze the claim language in the context of the claim and in view of the specification, and then if necessary, look elsewhere for support. Lowy did not do this. We look at each of Lowy's arguments below.

(1) Isolated as Used in the Field of Virology

In its reply, Lowy states that in the field of virology "isolate" was used to refer to viruses identified by lysing cells containing the virus by homogenization or other methodology and contacting cells which exhibit a detectable effect in response to the virus with the lysate. ('774 Interference, Paper 132, page 48, lines 3-6). Importantly, Lowy has failed to indicate how this proposed definition fits in the context of Lowy claim 49. Rather, several articles or text chapters are provided from disparate sources not related to the production of isolated particles from a recombinant construct in a known host cell in an attempt to shoehorn the proofs into Lowy's overly broad interpretation of "isolating."

Lowy first urges that a 1990 article in the Lancet (LX 3592)[5] in which ebola virus was said to be "isolated" from monkeys imported into the United States supports the broad interpretation of the word "isolate." ('774 Interference, Paper 132, page 48). The procedure is set forth in the article in some detail.

However, the procedure as outlined in the Lancet article is not adequately explained by Lowy. Lowy offers no expert testimony relating the article to the terms used in claim 49. We therefore have no evidence why isolation of a virus in the wild would be pertinent to the isolation as used in Lowy claim 49.

For example, we are not informed where the viruses are in each step. Is the "clarified" homogenate clarified by separating out the virus from cellular debris? Without more explanation, it appears to us that this type of isolation may involve removing the virus from at least part of the homogenate, which is more than an identification of the virus by a disruption of cells and contacting that cell lysate with cells sensitive to the virus. We decline to ferret out an explanation by wading through the article on Lowy's behalf.

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[5] The Lancet, 335:502-505 (1990)

As discussed by Dr. Schiller, the amount of separation needed depends upon the context in which the isolation is being conducted as to whether something has been isolated sufficiently. Lowy has additionally not explained how isolating cells for identification by immunofluorescence and electron microscopy equates to isolating for the purposes of raising high-titer antibodies.

We next turn to LX 3593, an article from the journal of Virology[6] placed into the record by Lowy. ('774 Interference, Paper 132, page 48). It states, in pertinent part:

> Isolation of VZV from lung tissues. Lungs were removed, minced finely with razor blades, washed two times by low-speed centrifugation in Williams medium E (GIBCO Laboratories) plus 20% fetal bovine serum, resuspended in medium with 2% fetal bovine serum, and applied in 1-ml volumes to drained MRC-5 cells in 25-cm^2 flasks. These were incubated for 4 h at 35°C, drained, and fed with 2 ml of Williams medium E plus 2% fetal bovine serum and 50 μ.g of neomycin per ml (twice per week). When viral plaques were visible, the cultures were trypsinized for cell-associated transmission to fresh cells. After several in vitro passages of each isolate, infected-cell suspensions were inoculated again into *C. Jacchus*.

Again, Lowy has failed to explain adequately how this passage from this article supports its position. Where are the viruses vis-a-vis the lung tissues from which they are "isolated?" What is involved in trypsinizing the cultures and

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[6] J. Virology 61:2951-2955 (1987) at 2952.

the "several in-vitro passages of each isolate?" Is something physically removed, or not? Lowy simply concludes that this article describes isolation of viruses by disrupting the cells containing the virus and contacting cells sensitive to the virus without providing any explanation of its reasoning or support, or how it relates to claim 49 - isolating particles for the purposes of raising high-titer antibodies, the context in which Lowy is isolating VLPs. We decline to speculate as to whether this article supports Lowy's conclusory statements.

We turn now to Lowy's third article submitted in support of its theory, LX 3594. This is another Journal of Virology[7] article, which states at pages 4044-4045 the following:

> Virus isolation. Peripheral-blood mononuclear cells from the two seropositive mandrils (2 x 10^6 cells per ml) were stimulated with 25 μg of concanavalin A per ml for 24 h and cultured in RPMI 1640 growth medium supplemented with 20% heat-inactivated fetal calf serum, antibiotics, and 10% crude interleukin-2. After cultivation for 3 to 7 days, these mandrill cells were cocultivated with Molt-4 clone 8 cells (23), which are highly susceptible to HIV-1 infection and its cytopathogenicity. After cocultivation, the medium without interleukin-2 was replaced every 3 days, and the cultures were examined for the expression of cytopathic effects (CPE). The expression of viral proteins in cultured cells was detected by immunofluorescence assay as described previously (28). The release of virus particles was examined by reverse transcriptase (RT) assay (28) and electron microscopy.

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[7] J. Virology 62:4044-4050 (1988)

Again, Lowy has provided no explanation of the relevance of this outlined procedure. Lowy has pointed to no testimony by anyone qualified to explain how those of ordinary skill in the art would understand the procedure outlined above to be "isolation" comparable to the isolation required by the claim. We are not informed of the state of the viruses (e.g. are the viruses in the supernatant what Lowy is saying are isolated, or is it the viruses in the cultured cells detected by immunofluorescence assay which are isolated?). We again decline to speculate how this article relates to Lowy claim 49 - isolating particles which are to be used functionally for raising high-titer antibodies.

Lowy Exhibit LX 3595, pages 7-8, is an excerpt from a textbook with a section on isolating viruses.[8] It notes that:

> The Isolation of Animal Viruses
> Many techniques have been developed for isolating viruses. The source of virus may be excreted or secreted material, the bloodstream, or some tissue. Samples are collected and, unless processed immediately, are sheltered from heat, preferably by storage at -70C, the temperature of dry ice. If necessary, a suspension is then prepared by grinding or sonicating in the presence of cold buffer solution, and **this is then centrifuged in order to remove large debris and contaminating microorganisms.**
>
> ...

[8] W.K. Joklik, Virology, (2d Ed.1985).

> The final stage of the isolation procedure is **passage at limiting dilution in order to ensure that only a single unique virus is being isolated. This** may be accomplished either by limiting serial dilution, when the virus suspension is diluted to such an extent that only one out of several aliquots inoculated gives a positive response, or by plaque isolation [emphasis added]

This text notes the function of centrifugation to remove large debris and contaminating microorganisms. This procedure includes homogenization and identification, but it also includes additional steps such as a final passage at a limiting dilution to ensure only one virus is being passed. Lowy has again not explained where the virus is relative to the cell which produced it, or if these additional steps not described by Lowy are necessary to "isolate" the virus, within its proposed meaning, and as it relates to claim 49.

Lowy points to exhibit LX 3596[9] as describing the isolation of rhabdoviruses. ('774 Interference, Paper 132, page 48). The exhibit describes a fourteen step procedure with the pertinent parts reproduced below:

> 3.1 Animal Rhabdoviruses
>
> ...
>
> (i) To isolate virus, prepare a 10% suspension of infected brain tissue, using MEM-10 as diluent, by homogenisation in a Ten Broeck homogeniser or by grinding with a pestle and mortar...

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[9] B.W.H Mahy, Virology: A Practical Approach (1985) pp.87

(ii) **Clarify the suspension by centrifugation (1600 r.p.m. for 10 min)** in a refrigerated centrifuge, collect the supernatant and test for sterility. Store the clarified suspension at low temperature (-70°C).

(iii) Prepare a suspension of freshly trypsinised BHK/21 cells in MEM-10 at a concentration of 1 x 10^6 cells per ml. A T-75 tissue culture flask generally has 20 x 10^6 cells in a confluent monolayer.

(iv) To isolate rabies virus, for example, mix 1 ml of BHK/21 cell suspension with 0.25 ml of brain suspension in a T-25 flask and let this stand for a few minutes.

(v) Add 5 ml of MEM-10, mix and transfer 0.5 ml amounts of virus-cell suspension to individual wells of an 8-chamber Lab-Tek tissue culture slide.

(vi) Incubate the cells in the T-25 flask and Lab-Tek slide at 37°C.

(vii) **Change the medium after 24 h to remove brain tissue debris.**

...

(xi) Trypsinise the cells, suspend them in 2 ml of MEM-10, return 0.5 ml of cells to T-25 flasks (1:4 split) and add 5 ml of MEM-10. [emphasis added]

Again, Lowy has not explained how the detailed 14 step procedure, involving clarification and a separate removal of brain tissue (see steps (ii) and (vii)(first occurrence)) supports Lowy's position that isolation is as broad as lysing and detecting without some form of separation. We do not see how this helps Lowy define "isolating" so broadly; nor how it relates to the use of the term in Lowy claim 49.

Lowy urges that in all of these isolation procedures, the viruses are physically separated from their natural environment - to Lowy's way of thinking, they are "dissociated from" at least some of its cellular materials which are found in intact cells, but not fully purified. ('774 Interference Paper 132, page 48). Lowy argues that "isolated virus" differs from "purified virus" in that "purified virus" is said to be obtained by a series of steps which concentrate the virus followed by purification on a centrifuge on a sucrose density gradient. ('774 Interference, Paper 132, page 48). Lowy argues that "isolation" does not require "purification."

Lowy cites for support of this distinction LX 3596 and LX 3597. LX 3596 describes, at pages 88-90 a detailed mechanism for purifying viruses. LX 3597[10] describes isolation of virus from clinical material. While they provide evidence that obtaining purified viruses may involve more steps than "isolating" viruses, neither of these references supports Lowy's proposed interpretation of "isolated" in that they describe only what a "purified" virus may be when completely purified.

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[10] J.M. Hoskins, Virological Procedures (1967).

We observe that purified viruses are also isolated viruses, having been separated from contaminants as well as cells. Simply because there exists a more restrictive class of separated viruses does not change the underlying requirement that the viruses must be separated to be isolated. Lowy has, instead of directly addressing the issue of what "isolated" means in the context of Lowy claim 49, argued that "isolated" is not the same as "purified."

In any event, we have no way of evaluating how one of ordinary skill in the art would view these articles. Lowy has not favored us with testimony from one skilled in the art explaining how these articles relate to the terms "isolated" and "isolating" as they appear in claim 49. When comparing them against the claim, the specification, and the dictionary definitions, all of which are similar, we find that all of the evidence of record points instead to "isolate" as requiring a degree of separation.

Indeed, this reliance on these articles in the reply brief is further indication that the heart of Lowy's argument is not founded in evidence, but merely attorney argument. Attorney argument cannot take the place of evidence. In re Scarborough, 500 F.2d 560, 566, 182 USPQ 298, 302 (CCPA 1974). Lowy urges that the homogenization step results in isolation because the

particles are separated from things with which they are normally associated. Lowy has not, however, chosen to clearly identify to us those cellular components from which the VLPs were actually removed such that they should be said to be "dissociated from" and consequently "separated" and therefore "isolated."[11]

(2) The Board's Decision on Preliminary Motions

Lowy urges that Lowy's construction of "isolated" is "[f]ully [s]upported" by the Board's decision on preliminary motions. (Paper 132, page 49, lines 18-19). In support of its position, Lowy states that the Board's opinion (Paper 149, page 69, first paragraph) stated that isolated papillomavirus capsids include papillomavirus capsids that have been purified. Lowy urges that its definition, encompassing VLPs which are separated from their natural environment, is "entirely consistent" with the Board's statement.

This argument misses the point as Lowy is again comparing apples and oranges. The Board included purified papillomavirus capsids as a type of "isolated" VLPs. This does not mean that

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[11] It is also worthy of noting that Dr. Monticello's testimony regarding the electron micrographs refutes Lowy's contention that the micrographs somehow dissociated the VLPs from anything and thus "isolated" the VLPs. The VLPs were said to be discernable in their proper locations relative to cell structures - preferentially located in the nucleus (LX 3402, paragraphs 11 and 12).

the Board's decision in Paper 149 in any way "[f]ully [s]upported" Lowy's unrelated and unreasonably broad definition of "isolated." Consequently, we reject Lowy's argument that the Board's decision on preliminary motions supports Lowy's definition of isolating.

(3) Lowy '181's specification

We have above noted the locations where Lowy's specification uses the word "isolated." These locations support a conclusion that Lowy's claim 49 includes physically separating the VLPs from the producing cells for the functional purpose of providing the claimed "isolated" VLPs that are capable of raising high-titer antibodies. We have discussed above that the prosecution history of Lowy '181 also supports this conclusion.

Lowy however now urges for the first time in its Reply Briefs that:

> **Lowy's specification also discloses the isolation of cell lysates which were used to immunize rabbits. See Lowy specification at 19, lines 34-36.** Such cell lysates were prepared by breaking the cells open, thereby disrupting the association of materials inside the cells with one another and generating a mixture in which the cellular contents are randomly distributed. Accordingly, in the preparation of these cell lysates, **the VLPs within the cells were separated from their natural environment (e.g., dissociated from at least some of the materials with which they are normally associated in intact cells). These cell lysates were also "isolated" within the ordinary meaning of the term.** ['774 Interference, Paper 132, page 51, lines 13-20][emphasis added].

This argument is misdirected in that the Lowy '181 specification does not use the word "isolation" or "isolate" at the location indicated by Lowy. Rather, Lowy '181 states:

> Rabbits were immunized by subcutaneous injection either with whole cell Sf-9 lysates ($3x10^7$ cells) prepared by one freeze/thaw cycle and 20x dounce homogenization(rabbit #1,2,and 8) or with 20 µg of L1 protein partially purified by differential centrifugation and 35% ammonium sulfate precipitation (#3,4,6, and 7), in complete Freund's adjuvant, and then boosted twice at two week intervals, using the same preparations in incomplete Freund's adjuvant. (LX 3051, paragraph spanning pages 19-20)

Thus, this passage discloses the immunization of rabbits using an unpurified whole-cell lysate that has not been separated into distinct components. In other words, the VLPs used to inoculate the rabbits were not "isolated" as we have construed that term in claim 49.

Lowy's argument in this respect is demonstrably circular. Lowy takes the position that this lysis outlined in the specification is "isolation" because Lowy would like us to accept that making a whole cell lysate somehow isolates the VLPs as required by claim 49. This argument is not persuasive evidence that the term should be given the meaning Lowy proposes. Indeed, the specification itself suggests that something more than cell lysis is required to "isolate" the particles.

(4) The Federal Circuit's Interpretation of Isolation

Lowy urges that its proffered definition of the term "isolated" in the field of virology has been approved by the Federal Circuit in its decision in Boehringer Ingelheim Vetmedica, Inc. V. Schering-Plough Corp., 320 F.3d 1339, 1347, 65 USPQ2d 1961,1964-1965 (Fed. Cir. 2003). ('774 Interference, paper 132, page 49).

Lowy states that in Boehringer Ingelheim the Federal Circuit affirmed the district court's construction of "isolating" which was based upon the definition of "isolate" in the Random House College Dictionary as "to set or place apart, detach or separate." *Id.* at 1346, 65 USPQ2d at 1965.

First, we observe that Lowy has again gone afield from the claim and specification of Lowy '181 in search of support. The context of the Boehringer Ingelheim decision is not the same as the context of Lowy claim 49. Nevertheless, Lowy concludes that the Federal Circuit construed "isolation" to mean separation or detachment from other materials, but did not require that the "isolated" materials be fully purified from all other materials.

Lowy does not explain how this construction supports its position. At best, it could be said that the Federal Circuit approved the use of a general dictionary in interpreting the meaning of "isolation" in the particular context of the

Boehringer Ingelheim case. We do not see the Federal Circuit's position as supporting Lowy's much broader interpretation, however.

Additionally, to the extent the Random House definition utilized in the district court's opinion may have any applicability in helping to determine the scope of the term "isolated", the Boehringer Ingelheim definition supports the interpretation of the term "isolate" as requiring some separation from other materials.

(5) Dr. Schiller's and Dr. Howley's Testimony

Lowy asserts that Dr. Schiller's testimony provides further support for its interpretation of the term "isolated." Lowy states that Dr. Schiller's testimony provides that the terminology "isolated" encompasses separating from the things with which it is normally associated to some degree. (LX 3475 at page 156 line 11 - page 157, line 1). Thus, Lowy concludes that Dr. Schiller's testimony actually supports a broad interpretation of the term "isolated" in which a material need only be separated from its natural environment, e.g. by lysing. ('774 Interference, Paper 123, page 52, second paragraph).

Dr. Schiller's complete quotation is previously reproduced herein. In sum, he stated that "isolation" meant separating the VLPs from other cellular proteins. (LX 3475, pages 156-157).

Lowy has not shown how this statement requiring "separation" supports that lysing host cells is "isolation" of the particles. Furthermore, this statement is not in the claim context.

(6) Summary of the "Isolation" Issue

We give the term "isolated" and "isolating" as used in Lowy's claim 49 their broadest reasonable interpretations in light of the entire claim and Lowy's disclosure. Lowy's proposed definition, while certainly broad, is not reasonable on this record. On balance, weighing the alternative possible definitions, we hold that a definition of isolation as requiring some removal, or separation, from the cells which produced the particle, is the correct one.

Considering the words of the claim, with reference to the specification, prosecution history, and then extrinsic evidence, including standard definitions, and the testimony of witnesses leads us to conclude that one of ordinary skill in the art at the time Lowy's application was filed, would recognize that "isolated" and "isolating" require physically separating the VLPs from the producing host cells, for the claim's functional purpose of providing "isolated" VLPs capable of raising high-titer antibodies, as discussed above.

C. **Lowy's Evidence - Isolation (Elements "A" and "F")**

Additional Findings of Fact

F774-20; F775-20. Lowy avers that Lowy infected cells with BPV recombinant L1 baculoviruses, and fixed samples of those cells in a formaldehyde and glutaraldehyde-based fixative for thin sectioning and examination by electron microscopy, sending them to Dr. Monticello before December 19, 1991. (Lowy Declaration, LX 3381, paragraphs 26 and 29)

F774-21; F775-21. Lowy avers that, on December 19, 1991, Dr. Monticello observed in the electron micrographs virus-like particles which were circular structures of approximately 50 nm in the 80 nm thin sections of insect cells. (Monticello Declaration, LX 3402, paragraph 11)(Micrographs, LX 3339-3347)

F774-22; F775-22. Lowy avers that the VLPs of F774-21 and F775-21 were observed in the nucleus (Monticello Declaration, LX 3402, paragraph 12)(Micrographs, LX 3339-3347).

F774-23; F775-23. Lowy avers that, in early 1992, Lowy had rabbits immunized by subcutaneous injection of whole-cell Sf9 lysates prepared by two freeze/thaw cycles and 20 strokes in a Dounce homogenizer of L1 recombinant- or wild type-infected Sf9 cells, and then boosted the rabbits by two booster injections at

2-week intervals (LX 3385, paragraph 107); See also Lowy (LX 3381); Schiller (LX 3383), and Kirnbauer (LX 3300), each at paragraph 70.

(I) Lowy's Alleged Conception - December 19, 1991

As noted above, a party seeking to establish conception must prove formation, in the mind of the inventor, of a definite and permanent idea of the **complete** invention as it is thereafter to be applied in practice. Lowy urges that if the Board should find that there is a "reasonable expectation" that the claimed result would occur upon obtaining a biological material, then Lowy conceived the invention on December 19, 1991 when Lowy visualized its virus-like particles in an electron micrograph. ('775 Interference, page 6, last paragraph).

In support of Lowy's conception argument, Lowy initially urges that Lowy "constructed" elements A, D, E, and F by December 19, 1991. ('775 Interference, Paper 167, page 14, last paragraph). Elements A, B, C, D, E and F are:

> [A] Isolated papillomavirus-like particles comprising an L1 polypeptide
>
> [B] which contains at least one conformational epitope
>
> [C] and is capable of inducing high-titer neutralizing antibody,
>
> [D] produced by the method comprising: permitting a genetic construct, comprising a papillomavirus L1 gene,

> [E] to direct recombinant expression and self-assembly of papillomavirus-like particles comprising the L1 polypeptide in a transformed eukaryotic host cell;
>
> [F] and isolating said self-assembled particles.

As evidence of alleged conception relating to elements (A) and (F) (the isolation aspect), Lowy states that:

> Dr. Monticello isolated the VLPs for visualization by thin sectioning of insect cells. Howley ¶ 66; Roden ¶ 25; Inventors ¶ 29; Monticello ¶ 12 ('774 Interference, Paper 123, page 16, line 15-16; Paper 132, page 20, line 7).

and

> The EM [electron microscope] prints, on their face, show to one of ordinary skill in the art that the Lowy team produced isolated particles that were of the correct size and shape to be VLPs. Howley ¶¶ 64, 67, 103, 106; Roden ¶¶ 23, 26, 62, 65. Thus, by December 19, 1991, Lowy had constructed the elements (A), (D), (E), and (F) above. ('774 Interference Paper 123, page 17, lines 4-6).

As Lowy's evidence of "isolation" in Lowy's alleged conception, Lowy cites the First Declaration of Howley, LX 3385, ¶ 66, Second Declaration of Roden, LX 3396, ¶ 25, Inventors, Third Declaration of Lowy, LX 3381, First Declaration of Schiller, LX 3383, and First Declaration of Kirnbauer, LX 3300, all to ¶ 29, and First declaration of Monticello, LX 3402, ¶ 12. As discussed below, none of these paragraphs constitute persuasive evidence.

We look at Dr. Howley's declaration, LX 3385 first. Dr. Howley is proffered as an expert witness and, as evidenced by paragraphs 3-5, appears to be well-qualified in the field of papillomaviruses.

Dr. Howley states that:

> 66. The VLPs were isolated in the sense that circular structures of approximately 50 nm were isolated for visualization by thin sectioning of insect cells in thin sections I understand to be approximately 100 nm thin sections.

This statement is not persuasive. First, Dr. Howley has not pointed us to a place in the record where support for these assertions can be found. For example, we cannot tell how the expert witness knows that these events took place. We decline to act as advocate for Lowy and go hunting about in the record for evidence to support Lowy's position.

To the extent Dr. Howley may be relied upon as an expert witness in defining thin-sectioning of insect cells as "isolating," we accord this testimony little persuasive weight because it does not address the term "isolate" in the context of Lowy claim 49. No persuasive reasoning for this interpretation of the term as encompassing thin sectioned slices as "isolating" the VLPs, which slices were prepared for electron micrography, is provided. We do not credit these unsupported conclusions or

conclusory statements without supporting persuasive reasoning and evidence.

We next turn to the Second Declaration of Richard B. Roden, Ph.D., LX 3396, ¶ 25. Dr. Roden, like Dr. Howley, appears qualified as an expert in the field of papillomaviruses by virtue of his experience outlined in paragraphs 2 through 5 of his declaration.

Dr. Roden also, like Dr. Howley, states:

> 25. The VLPs were isolated in the sense that circular structures of approximately 50 nm were isolated for visualization by thin sectioning of insect cells in thin sections I understand to be approximately 100 nm thin sections.

It quickly becomes apparent that these paragraphs are identical. Consequently, and as discussed above with reference to Dr. Howley, this statement is also not persuasive.

We turn next to the third Declaration of Lowy, LX 3381, paragraph 29. In it, Dr. Lowy (an inventor) states:

> 29. The VLPs were isolated in the sense that circular structures of approximately 50 nm were isolated for visualization by thin sectioning of insect cells in thin sections we understood to be approximately 100 nm thin sections.

Again, this paragraph in Dr. Lowy's declaration is a verbatim copy of the corresponding paragraphs of Drs. Howley and Roden. It suffers from the same infirmities that the previous declarations suffer from.

We turn next to the First Declaration of Dr. John T. Schiller, Ph.D. (a joint inventor), LX 3383, paragraph 29, and to the First Declaration of Reinhard Kirnbauer (a joint inventor), LX 3300, also paragraph 29. In it, Drs. Schiller and Kirnbauer state (respectively):

> 29. The VLPs were isolated in the sense that circular structures of approximately 50 nm were isolated for visualization by thin sectioning of insect cells in thin sections we understood to be approximately 100 nm thin sections.

This paragraph is unpersuasive (vis-a-vis Schiller and Kirnbauer) for the reasons Dr. Lowy's paragraph is unpersuasive, recited above.

Finally, we turn to the First Declaration of Thomas Monticello, D.V.M., Ph.D. (a witness) LX 3402, paragraph 12. In it, he states that from August 1990 to June 1992, he was a pathologist in the Electron Microscopy Section at Pathology Associates, Inc., Durham, North Carolina ("PAI"), and that he is an anatomical pathologist, retained as a consultant by Lowy. (Paragraphs 3-6).

Dr. Monticello states:

> 12. The virus-like particles were isolated in the sense that circular structures of approximately 50 nm were isolated for visualization by thin sectioning of insect cells in 80 nm thin sections.

Dr. Monticello, like the above witnesses, has provided no explanation as to how he reached his conclusion in paragraph 12 as to why this sectioning can properly be considered to be "isolation." This is especially true as Lowy's principal argument for "isolation" appears to be that the VLPs are "disassociated" from things in the cell which they are normally associated with. If Dr. Monticello observed the VLPs within the nucleus, where they belong naturally, then we are skeptical that any meaningful "dissociation" has taken place.

This lack of dissociation is further supported by the testimony of Dr. Jack Griffith, alleged to be an expert in the field by Lowy ('774 Interference, Paper 132, page 14, line 3). In arguing for visualization and identification of VLPs in Lowy's thin sections, Dr. Griffith observed that the "P-L particles are present in the nuclei of the cells infected with the recombinant baculovirus expressing the L1 protein, and it is known that papillomavirus assembly occurs in the nucleus of infected cells" ('774 Interference, Paper 132, page 14, lines 10-12)(See also LX 3580, page 1, last paragraph; page 3, last paragraph; and Conclusions, page 6, point 2). If the thin sections of cells are reasonably preserved such that the major structures of the cell and locations vis-a-vis each other are retained, we are not persuaded that the VLPs have been sufficiently dissociated from

their surroundings such that they can be considered to have been "isolated." For this additional reason, we find that Dr. Monticello's thin sections have not been "isolated" within the meaning of the count.

The identical wording of these paragraphs, along with their unsupported nature, cause us to question the credibility of these witnesses in that very little independent thought seems to have been given to their declarations. Collaboration on presentation of their testimony may have occurred. We, therefore, accord these witnesses little credibility and give their testimony little weight on these issues.

In the '774 Interference, Paper 123, page 17 ('775 Interference, Paper 167, page 16), Lowy also states:

> The EM [electron microscope] prints, on their face, show to one of ordinary skill in the art that the Lowy team produced isolated particles that were of the correct size and shape to be VLPs. Howley ¶¶ 64, 67, 103, 106; Roden ¶¶ 23, 26, 62, 65. Thus, by December 19, 1991, Lowy had constructed the elements (A), (D), (E), and (F) above.

Lowy appears to offer micrographs as evidence supporting all limitations of the count except for the existence of conformational epitopes and high titer neutralizing antibody induction. The specific micrographs referred to are not specifically identified in Lowy's priority brief. We look to Dr. Howley's (Lowy's expert) declaration, LX 3385, first to determine

which micrographs are being referred to and how those micrographs support Lowy's contention. Dr. Howley states, in the Lowy cited paragraphs:

> 64. On December 19, 1991, Dr. Monticello sent Lowy the results of examination by electron microscopy of thin sections of the samples. In comparison to the wild-type baculovirus infected cells, the cells infected with the BPV recombinant virus contained many circular structures of approximately 50 nm, which were preferentially localized in the nucleus of cells. These results indicated to Dr. Monticello, and Lowy affirmed, that self-assembly of L1 into VLPs had occurred, since in vivo papillomavirus virion assembly takes place in the nucleus and the diameter of the virions (spherical in shape) had been reported as 55 nm.
>
> 67. The electron micrographs indicated that the particles were the right size (50 nm) and shape (spherical) to be VLPs that mimicked papillomavirus virions morphologically (in terms of their appearance). Thus, Lowy reasonably believed that the VLPs might also mimic papillomavirus virions immunologically by being capable of inducing high-titer neutralizing antibodies.
>
> 103. In comparison to the wild type baculovirus-infected cells, the cells infected with the BPV recombinant virus contained many circular structures of approximately 50 nm, which were preferentially localized in the nucleus of cells. These results indicated that self-assembly of L1 into VLPs had occurred, since in vivo papillomavirus virion assembly takes place in the nucleus and the diameter of the virions (spherical in shape) had been reported as 55 nm (Howley, Chap. 30: "Papillomavirinae and Their Replication," Fundamental Virology 1991 at 744, col. 1:20) (LX. 3024).
>
> 106. As shown by the one-page fax from Dr. Kirnbauer to Dr. Monticello dated December 19, 1991 ("Thank you for the pictures, we are all very pleased about it.") (LX 3338), I understand that Lowy concluded that the electron micrographs indicated that self-assembly of L1 into VLPs had occurred, since in vivo papillomavirus virion assembly takes place in the nucleus and the diameter of the virions (spherical in shape) had been reported as 55 nm. I independently conclude

> that the electron micrographs indicated that self-assembly of L1 into VLPs had occurred, since in vivo papillomavirus virion assembly takes place in the nucleus and the diameter of the virions (spherical in shape) had been reported as 55 nm.

To the extent that paragraphs 64 and 67 do not provide citations to the record where support for Dr. Howley's conclusions may be found, we do not credit these statements with any evidentiary or probative value towards establishing that the electron micrographs show "isolated" VLPs. Dr. Howley has not testified that he witnessed the events related in paragraph 65 - at best, they are narrative to give context for his later remarks. We do not know on which electron micrographs Dr. Howley based his opinion in paragraphs 67 and 103. We do not know if the electron micrographs he refers to were part of the record at all. Even if we were to ascribe evidentiary value to these paragraphs, they do not show how the thin sectioning of the VLPs in the cell nucleus meets the limitation of the count for "isolated" self assembled particles.

Paragraphs 103 and 106 state, based on his review of the electron micrographs, that Dr. Howley concludes that the VLPs were formed in the nucleus. If the nucleus is intact, such that the VLPs are not, to borrow Lowy's phrase "disassociated" from things they are normally associated with, then Lowy has, even

under its own theory of the definition of "isolation" failed to show how these visualized VLPs were "isolated." Finally, paragraphs 103 and 106 do not show that the sectioned and fixed particles were operative for their intended purposes.

We next turn to the Second Declaration of Richard B. Roden, Ph.D., LX 3396. The Lowy cited paragraphs are virtually identical to the four Howley paragraphs reproduced above, with inconsequential numbering changes. They are unpersuasive for the same reasons as for Dr. Howley.

Conception requires the idea of the complete invention and possession of an operative method of making it. Nowhere has Lowy pointed us to a place in the record where a complete conception of the invention's "isolated" particles produced by a process including the concept of a step of "isolating" the self-assembled particles is to be found, as these terms are used in Lowy claim 49. As a consequence, we conclude that for at least this reason Lowy has not proven a conception on December 19, 1991.

Lowy urges that if the Board should find that there is a "reasonable expectation" that the claimed result would occur upon obtaining a biological material, then Lowy conceived the invention on December 19, 1991 when Lowy visualized its virus-like particles in an electron micrograph. Setting aside the "isolation" issue for now, Lowy has additionally failed to

persuade us that it had a reasonable expectation of achieving elements "B" and "C" of Lowy claim 49 - that the virus-like particle comprise an L1 polypeptide:

> [B] which contains at least one conformational epitope
>
> [C] and is capable of inducing high-titer neutralizing antibody.

Lowy believes it had a "reasonably expectation" of obtaining elements B and C because the VLPs seen in the micrographs "morphologically mimicked" the native virion (i.e. were the proper size and shape), were localized in the cell nucleus, and existed in appreciable numbers. According to Lowy, once these particles were visualized, Lowy believed that because the particles looked like native virions, they would contain conformational epitopes that induce high-titer neutralizing antibodies.

The only support for this conclusion is in the testimony of Lowy (LX 3381)(paragraph 30), Shiller (LX 3383)(paragraph 30), Kirnbauer (LX 3300)(paragraph 30), with the expert witnesses Howley (LX 3385)(paragraph 67) and Roden (LX 3300)(paragraph 30) weighing in as well. Their virtually identical testimony is as follows in the block quotation below (parentheticals show "expert" witness addition; brackets indicate the inventors' version):

> The electron micrographs indicated that the particles were the right size (50nm) and shape (spherical) to be VLPs that mimicked papillomavirus virions morphologically (in terms of appearance). Thus, [we] (Lowy reasonably) believed that the VLPs might also mimic papillomavirus virions immunologically by being capable of inducing high-titer neutralizing antibodies (emphasis added).

First, we are not provided with a clear citation to the evidence. Which electron micrographs, specifically, were any of the inventors or experts referring to by this paragraph? We do not know. Second, we are provided with no reasoning to support Lowy's theory that, if the particles looked right, there is a reasonable expectation that the particles would work immunologically. Neither the inventors, nor the expert witnesses, provide sufficient foundation for their conclusory statement that they believed, or it was reasonable for them to believe, that the VLPs would have conformational epitopes which would raise high-titer antibodies as required by elements "B" and "C" of Lowy claim 49 because the particles looked like VLPs.

Indeed, Lowy takes up much of its opening brief advocating a contrary position - that the processes involved in recombinant technology are so unpredictable that the evidence can only support simultaneous conception and reduction to practice in these interferences. ('775 interference, page 10, lines 6-9). Lowy further alleges, as regards the production of particles,

"[b]ecause morphology did not predict destiny, one would not be able to establish conformational epitopes of native virions until demonstrated through successful experimentation" ('775 interference, page 12, lines 12-14). Lowy again cites us to the testimony of its experts and inventors in support of this alternative conclusion. The inherent conflict in simultaneously advocating both positions significantly weakens the credibility of the inventors and experts. Accordingly, we do not credit their testimony on this point.

Furthermore, the conclusory nature of the testimony - that because the particles looked similar, there was a reasonable expectation that they would work, does not establish that Lowy had a reasonable expectation of achieving conformational epitopes which would raise high-titer antibodies. Why is it likely that they would work? In the experts's experiences, once one generated VLPs, how likely was it that they would have conformational epitopes which generated an immune response? We are denied this information by Lowy.

Consequently, we conclude that Lowy has not put forth persuasive evidence to convince us that Lowy reasonably expected that the particles visualized on December 19, 1991 would contain at least one conformational epitope and be capable of inducing high-titer neutralizing antibody. (Elements "B" and "C").

Accordingly, Lowy's alleged conception of December 19, 1991 fails for this additional reason.

We note that Lowy has not alleged or raised diligence at any time in its priority brief.

(II) Lowy's Alleged Actual Reduction to Practice March 26, 1992

To prove an actual reduction to practice which meets the count, the virus-like particles must have been "isolated" (element A), by "isolating the self assembled particles" (element F), have at least one conformational epitope (element B) and work for their intended purpose of raising high-titer neutralizing antibodies (element C). As discussed above, we have found that some physical separation from the host cells which created the VLPs must be achieved for the step of "isolating" to be met.

The elements of the count, as argued by Lowy, are again:

> [A] Isolated papillomavirus-like particles comprising an L1 polypeptide
>
> [B] which contains at least one conformational epitope
>
> [C] and is capable of inducing high-titer neutralizing antibody,
>
> [D] produced by the method comprising: permitting a genetic construct, comprising a papillomavirus L1 gene,

> [E] to direct recombinant expression and self-assembly of papillomavirus-like particles comprising the L1 polypeptide in a transformed eukaryotic host cell;
>
> [F] and isolating said self-assembled particles.

Lowy urges that it had constructed elements (A), (D), (E), and (F) in its December 19, 1991 electron micrographs. Lowy further urges that it constructed elements (B) and (C) by March 26, 1992. On that date, Lowy states that "the immune sera were able to reduce viral infectivity by 100% at a dilution of 1:1,600. ('774 Interference, Paper 123, page 21, lines 1-2).

As we have concluded that Lowy failed to show elements (A), (B), (C) and (F) in its alleged conception of December 19, 1991, we look to determine if it has proven all required elements on its alleged actual reduction to practice of March 26, 1992.

Lowy alleges that after visualizing VLPs on December 19, 1991, Lowy then states that Lowy then turned to testing the VLPS. Lowy states that on January 11, 1992 Lowy "isolated" VLPs for immunization by making whole cell lysates of insect cells. These "lysates" are said by Lowy to be prepared by lysing cells to expose the conformational epitopes on the VLP for immunization and generation of anti-VLP sera. Lowy further alleges that "extracts" were prepared of the L1 recombinant (VLP containing) and wild-type (control) infected Sf9 host cells. ('775

interference, paper 167, page 19). We observe that no direct reference to any notebook pages are found in the briefs.

These extracts apparently were inoculated (by a procedure not discussed in Lowy's brief) into rabbits on a date (not mentioned in Lowy's brief) by a party (not named in Lowy's brief). Subsequently (the date is not mentioned in Lowy's brief), anti-VLP sera was collected from the rabbits (by a procedure not mentioned in Lowy's brief). ('775 interference, paper 167, page 19).

Lowy alleges that a series of neutralization assays were conducted beginning on February 19, 1992 with a first neutralization assay. These assays are stated by Lowy to have been used to determine the presence of conformational epitopes and the ability to induce high-titer neutralizing antibodies. ('775 interference, paper 167, page 19). The first assay was said to have been completed March 10, 1992. ('775 interference, paper 167, page 20). The second neutralization assay was stated by Lowy to have been started on March 5, 1992 and completed by March 26, 1992 - resulting in 100% viral infectivity reduction at a dilution of 1:1,600. ('775 interference, paper 167, page 20). Other than expert or inventor testimony, in support of this point Lowy cites only LX 3021 and LX 3360. LX 3021 is the National Academy of Science article published in December, 1992. It is

not persuasive contemporaneous evidence of the alleged actual reduction to practice. LX 3360 appears to be a photograph of neutralization plates, but their significance remains inadequately explained in Lowy's priority brief. Are these original photographs, and how do they relate to the experiments which were conducted? Lowy begins to explain the photographs in its reply briefs, but that discussion occurs far too late.

We initially return to elements (A) and (F), the isolation aspect of Lowy claim 49.

Lowy urges, in support of its alleged actual reduction to practice on March 26, 1992 that:

> Upon visualizing VLPs by December 19, 1991, Lowy turned to the next step - testing the VLPs to determine if they could induce high-titer neutralizing antibodies. On January 11, 1992 **Lowy isolated VLPs for immunization by making whole-cell lysates of insect cells.** Extracts were prepared of L1 recombinant and wild-type (control) infected Sf9 cells. The cells were lysed to expose the conformational epitopes on the antigen (the VLP) for immunization and generation of anti-VLP sera. Howley ¶¶ 69, 70, 107 (*see* ¶¶ 71-83, 108-116); Roden ¶¶ 28, 29, 66 (*see* ¶¶ 30-42, 67-75); Inventors ¶¶ 32, 33, 70 (*see* 34-46, 71-79) (emphasis added). ['774 Interference, Paper 123, page 19, lines 17-20].

In attempting to corroborate Lowy's inventors' testimony with a written document, Lowy turns to an EIR (Employee Invention Report)

> The EIR also detailed Lowy's methodology. In the EIR Lowy described that it (1) constructed a genetic construct by placing the BPV L1 open reading frame in a baculovirus vector; (2) transformed a eukaryotic cell (insect cell); (3) permitted the construct to direct recombinant expression and self-assembly of VLPs comprising the L1 polypeptide; (4) isolated the VLPs; and (5) showed that the VLPs induced high-titer neutralizing antibodies and thus had conformational epitopes. Howley ¶¶ 81, 113, Roden ¶¶ 40, 72; Inventors ¶¶ 44, 76. The EIR, on its face, shows that Lowy constructed an embodiment that met every limitation of the count. ('774 Interference Paper 123, page 22, lines 13-19)

In support of this particular paragraph, Lowy has pointed us to about 125 paragraphs from two experts and three inventors. However, many of these 125 paragraphs are duplicates and unrelated to "isolation" or cell lysation. In fact, other than changing the numbers of the paragraphs, a great number of these paragraphs are <u>exact</u> duplicates of each other.

The only cited paragraphs which we have found which directly relate to the alleged "isolation" by lysation of the Sf9 cells are Howley (LX 3385) paragraphs 69, 81, and 107.

> 69. On January 11, 1992, Lowy made preparations of whole-cell lysates of L1 recombinant- and wild type-infected Sf9 insect cells.
>
> 81. On April 14, 1992, Lowy reported its success in an Employee Invention Report ("EIR"), signed by the inventors and co-signed by a non-inventor. In the EIR, Lowy reiterated that Lowy: (1) constructed a genetic construct containing a papillomavirus L1 gene; (2) transformed a eukaryotic cell (insect cell); (3) permitted the construct to direct recombinant expression and self-assembly of VLPs comprising

> the L1 polypeptide; (4) isolated the VLPs; and (5) showed that the VLPs induced high-titer neutralizing antibodies and thus had conformational epitopes.
>
> 107. As shown by a letter from Dr. Schiller to Dr. Hatgi dated January 13, 1992 (LX 3352), pages entitled "Rabbit #: 4665", "Rabbit #: 4666", and "Rabbit #: 4667" separate from the laboratory notebook (LX 3353-3355, respectively), and the page dated January 11, 1991 [sic, January 11, 1992] of the laboratory notebook (LX 3356), Lowy had rabbits immunized by subcutaneous injection of whole-cell Sf9 lysates prepared by two freeze/thaw cycles and 20 strokes in a Dounce homogenizer of L1 recombinant- or wild type-infected Sf9 cells, and then boosted the rabbits by two booster injections at 2-week intervals. I understand that submitted herewith as LX 3352 is a true and correct copy of the above-referenced letter.

Of these paragraphs, 69 and 81 fail to point us to the record for sufficient evidence to support Dr. Howley's conclusions. Moreover, Dr. Howley has not testified that he witnessed the events said to have occurred on those days. As such, we accord these paragraphs no weight. Only paragraph 107 provides any citations to the record.

Lowy claim 49 is an alternate definition of the count, and requires "isolated" particles prepared by a step of "isolating" the self assembled particles. We have interpreted this term at some length above, and it includes separating the particles from the host cell which produced them.

Howley paragraph 69 indicates that Lowy made whole-cell lysates of Sf9 cell. No explanation of how this meets any definition of "isolated" is given. Paragraph 81 simply parrots

the language "isolated" from another Lowy writing without providing any persuasive evidence or reasoning as to why the term should include the whole cell lysates.

Paragraph 107 of Howley reveals that the Sf9 lysates were prepared by "two freeze/thaw cycles and 20 strokes in a Dounce homogenizer." We can find no evidence of "isolation" as the term is used in Lowy claim 49 - i.e. separation of the self-assembled VLPs to provide isolated particles in this lysation. Accordingly, Lowy's contention that the VLPs were "isolated" is unsupported by Dr. Howley's conclusory testimony.

We next turn to the Second Declaration of Richard B. Roden, Ph.D., LX 3396, specifically, paragraphs 28, 29, 40, and 66, which relate to "isolation" by lysation. They are identical to the Howley paragraphs discussed above, and unpersuasive for the same reasons.

We next turn to the "Inventors" declarations, Lowy (LX 3381); Schiller (LX 3383), and Kirnbauer (LX 3300). The paragraphs cited by Lowy are 32, 33, and 70. Being inventors, the paragraphs are phrased slightly differently, i.e., in the first person plural:

> 32. On January 11, 1992, we made preparations of whole-cell lysates of L1 recombinant- and wild type-infected Sf9 insect cells.

> 33. On January 16, 1992, we immunized rabbits with the preparations and then gave them two booster injections at 2-week intervals.
>
> 70. As shown by a letter from Dr. Schiller to Dr. Hatgi dated January 13, 1992 (LX 3352), pages entitled "Rabbit #: 4665", "Rabbit #: 4666", and "Rabbit #: 4667" separate from Dr. Kirnbauer's laboratory notebook (LX 3353-3355, respectively), and the page dated January 11, 1991 [sic, January 11, 1992] of Dr. Kirnbauer's laboratory notebook (LX 3356), we immunized rabbits by subcutaneous injection of whole-cell Sf9 lysates prepared by two freeze/thaw cycles and 20 strokes in a Dounce homogenizer of L1 recombinant- or wild type infected Sf9 cells, and then boosted the rabbits by two booster injections at 2-week intervals. Submitted herewith as LX 3352 is a true and correct copy of the above-referenced letter.

We observe that not one of these three paragraphs supports the proposition that Lowy actually reduced to practice an embodiment of the count which includes "isolated" VLPs prepared by a step of "isolating" the self assembled particles from the host cells by separation. The Sf9 cell lysates, and resultant immunization and elicitation of an immune response, were not done with an "isolated" VLP, as defined the embodiment of the count represented in Lowy claim 49. Nor is there evidence that the VLPs were "isolated," as we have construed that term in claim 49, at any other stage of these experiments. We conclude that this evidence is insufficient to establish an actual reduction to practice proven on March 26, 1992, the date of completion of the second neutralization assay.

Lowy also relies on an Employee Invention Report (EIR) in support of its position that Lowy actually reduced to practice an embodiment of the invention within the count.

We look to the EIR itself, first, to see if there is support for point (4) - isolated the VLPs. The EIR, although not directly cited in Lowy's brief, is LX 3312, and states, in pertinent part:

> B/C OUR INVENTION: We have succeeded in making virus-like BPV particles that, when inoculated in rabbits, induce high levels (>1:10,000) of neutralizing antibodies. This has been achieved using only BPV L1 (without L2), expressed in insect cells, using a baculovirus (insect virus) vector. (LX 3312, Paragraph spanning pages 2 and 3)
>
> . . .
>
> Our Method: The BPV L1 open reading frame was placed in a baculovirus vector in place of the viral polyhedron gene. The resulting virus was used to infect Sf-9 insect cells. Several days after infection, electron micrographic analysis of thin sections of cells showed many 45 nm virus-like particles (and fibrous sheets) that were not seen in cells infected with the parental baculovirus (that did not contain BPV L1). **L1 protein was identified immunologically in cell extracts. Rabbits were inoculated with extracts from cells expressing the L1 protein and from cells expressing the parental virus.** Sera from rabbits were tested at various dilutions for their ability to prevent infection of mouse cells by BPV particles. BPV infectivity was measured by focus formation. (LX 3312, Page 3, second paragraph from bottom). (Emphasis added)

We remain uncertain what these "extracts" are - all the evidence of record so far describes cell lysates. We turn to the cited testimony of the inventors first, in this instance, to find more information about what these "extracts" were.

Inventors Lowy (LX 3381); Schiller (LX 3383), and Kirnbauer (LX 3300) cited paragraph 44 states:

> 44. On April 14, 1992, we reported our success in an Employee Invention Report ("EIR"), signed by us as the inventors and co-signed by a non-inventor. In the EIR, we reiterated that we: (1) constructed a genetic construct containing a papillomavirus L1 gene; (2) transformed a eukaryotic cell (insect cell); (3) permitted the construct to direct recombinant expression and self-assembly of VLPs comprising the L1 polypeptide; **(4) isolated the VLPs**; and (5) showed that the VLPs induced high-titer neutralizing antibodies and thus had conformational epitopes. (Emphasis added).

Cited paragraph 76 states:

> 76. As shown by the Employee Invention Report signed by us as the inventors and co-signed by a non-inventor April 14, 1992 ("We have succeeded in making virus-like **BPV particles that, when inoculated in rabbits**, induce high levels (>1:10,000) of neutralizing antibodies. ...

Neither of these paragraphs supports Lowy's assertion that it "isolated" the VLPs, as required by the count. Paragraph 44 merely asserts that the VLPs were isolated without explaining how this occurred. Paragraph 76 explains that the VLP particles were inoculated into the rabbits, but does not explain how those particles were prepared. As a consequence, the inventor testimony does not explain that these "extracts" included VLPs

which were isolated.

We note that the inventor declarations discuss these "extracts" at several locations, including paragraphs 22, 36, 39, 72, 74, 75, 76, and 77, but do not describe what is meant by "extract." Accordingly, we have no way of knowing what this extract is, and whether it is different from the cell lysates, which we have found not to be "isolated" VLPs.

Howley (LX 3385), paragraphs 81 and 113, and Roden (LX 3396) paragraphs 40, 72 are also cited to us by Lowy in support of the position that these extracts were isolated VLPs.

Howley paragraph 81 and 113 read as follows (Roden paragraphs 40 and 72 are virtually identical, with differing paragraph numbers and placing them in the third person)(bold emphasis added):

> 81. On April 14, 1992, Lowy reported its success ....In the EIR, Lowy reiterated that Lowy: (1) constructed a genetic construct ... **(4) isolated the VLPs** ...
>
> 113. As shown by the Employee Invention Report signed by the inventors ...

Paragraph 81 is, again, an unsupported conclusory statement that the VLP's were isolated, and paragraph 113 provides no description of the manner in which the VLPs were prepared for inoculation into the rabbits. Accordingly, Dr. Howley's and Dr. Roden's testimony offers no further support. The EIR does not

provide persuasive evidentiary support for Lowy's position that the VLPs were isolated within the meaning of Lowy claim 49.

We conclude, based upon the evidence of record, that Lowy has not established Lowy claim 49 elements A and F of its conception or reduction to practice in that Lowy has not shown that its VLPs were isolated, or that a step of isolating the self-assembled VLPs from the host cell occurred.

As Lowy has argued for conception simultaneous with actual reduction to practice, we also hold that Lowy has failed to demonstrate that the inventors possessed a reasonable expectation of obtaining the desired isolated VLPs. Accordingly, Lowy has failed to demonstrate by a preponderance of the evidence that its inventors conceived of an invention within the scope of Lowy claim 49 by March 26, 1992.

V. CONCLUSION

Accordingly, Lowy has not demonstrated a conception or reduction to practice as of its March 26, 1992 date. Neither has Lowy demonstrated a conception as of its December 19, 1991 date. Thus, Lowy cannot prevail on priority Against Frazer or Schlegel as Lowy has not shown a conception or reduction to practice prior to either Schlegel's or Frazer's accorded benefit dates. Lowy then does not prevail in the 104,774 or 104,775 interferences.

/ss/ Fred E. McKelvey FRED E. McKELVEY, Senior Administrative Patent Judge	
/ss/ Sally Gardner Lane SALLY GARDNER LANE Administrative Patent Judge	BOARD OF PATENT APPEALS AND INTERFERENCES
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APPENDIX A

Webster's New Collegiate Dictionary, 1978

\is-'läm-ik, iz-, -'lam-\ *adj* — **is-lam-ics** \-iks\ *n pl but sing or pl in constr*
is-lam-ism \is-'läm-,iz-əm, iz-'läm-, -'lam-; 'iz-ləm-\ *n* : the faith, doctrine, or cause of Islam — **is-lam-ist** \-əst\ *n*
is-lam-ize \'iz-lə-,mīz; is-'läm-,īz, iz-'läm-, -'lam-\ *vt* **-ized; -iz-ing** : to make Islamic; *esp* : to convert to Islam — **is-lam-i-za-tion** \,iz-lə-mə-'zā-shən; is-,läm-ə-, iz-,läm-, -,lam-\ *n*
¹is-land \'ī-lənd\ *n* [alter. of earlier *iland*, fr. ME, fr. OE *īgland*; akin to ON *eyland* island; both fr. a prehistoric NGmc-WGmc compound whose first constituent is represented by OE *īg* island (akin to OE *ēa* river, L *aqua* water) and whose second constituent is represented by OE *land*] **1** : a tract of land surrounded by water and smaller than a continent **2** : something resembling an island esp. in its isolated or surrounded position **3 a** : SAFETY ISLAND **b** : SAFETY ZONE **4** : a superstructure on the deck of a ship (as an aircraft carrier) **5** : an isolated group or area; *esp* : an isolated ethnological group
²island *vt* **1 a** : to make into or as if into an island **b** : to dot with or as if with islands **2** : ISOLATE
is-land-er \'ī-lən-dər\ *n* : a native or inhabitant of an island
island universe *n* : a galaxy other than the Milky Way
¹isle \'ī(ə)l\ *n* [ME, fr. OF, fr. L *insula*] : ISLAND; *esp* : a small island
²isle *vt* **isled; isl-ing** **1** : to make an isle of **2** : to place on or as if on an isle
is-let \'ī-lət\ *n* : a little island
islet of Lang-er-hans \-'läŋ-ər-,hänz, -,hän(t)s\ [Paul *Langerhans* †1888 G physician] : any of the groups of small slightly granular endocrine cells that form anastomosing trabeculae among the tubules and alveoli of the pancreas and secrete insulin
-ism \,iz-əm\ *n* [*-ist*] : a distinctive doctrine, cause, or theory
-ism \,iz-əm\ *n suffix* [ME *-isme*, fr. MF & L; MF, partly fr. L *-isma* (fr. Gk) & partly fr. L *-ismus*, fr. Gk *-ismos*; Gk *-isma* & *-ismos*, fr. verbs in *-izein* -ize] **1 a** : act : practice : process ⟨criticism⟩ ⟨plagiarism⟩ **b** : manner of action or behavior characteristic of a (specified) person or thing ⟨animalism⟩ **2 a** : state : condition : property ⟨barbarianism⟩ **b** : abnormal state or condition resulting from excess of a (specified) thing ⟨alcoholism⟩ or marked by resemblance to (such) a person or thing ⟨mongolism⟩ **3 a** : doctrine : theory : cult ⟨Buddhism⟩ **b** : adherence to a system or a class of principles ⟨stoicism⟩ **4** : characteristic or peculiar feature or trait ⟨colloquialism⟩
isn't \'iz-ənt\ : is not
iso-ag-glu-ti-na-tion \'ī-(,)sō-ə-,glüt-ᵊn-'ā-shən\ *n* : agglutination of an agglutinogen of one individual by the serum of another of the same species — **iso-ag-glu-ti-na-tive** \-'glüt-ᵊn-,āt-iv\ *adj*
iso-ag-glu-ti-nin \,ī-(,)sō-ə-'glüt-ᵊn-ən\ *n* : an agglutinin specific for the cells of another individual of the same species
iso-ag-glu-tin-o-gen \'ī-(,)sō-,ag-lü-'tin-ə-jən\ *n* : a substance capable of provoking formation of or reacting with an isoagglutinin
iso-al-lox-a-zine \,ī-(,)sō-ə-'läk-sə-,zēn\ *n* [*iso-* + *allantoic* + *oxalic* + *azine*] : a yellow solid $C_{10}H_8N_4O_2$ that is the parent compound of various flavins (as riboflavin)
iso-an-ti-body \,ī-(,)sō-'ant-i-,bäd-ē\ *n* : an antibody against an antigen present in some members of a species that is produced by a member of the species lacking that antigen
iso-an-ti-gen \-'ant-i-jən\ *n* [ISV] : an antigen capable of inducing the production of an isoantibody — **iso-an-ti-gen-ic** \'ī-(,)sō-,ant-i-'jen-ik\ *adj* — **iso-an-ti-ge-nic-i-ty** \-jə-'nis-ət-ē\ *n*
iso-bar \'ī-sə-,bär\ *n* [ISV *is-* + *-bar* (fr. Gk *baros* weight); akin to Gk *barys* heavy — more at GRIEVE] **1** : an imaginary line or a line on a map or chart connecting or marking places on the surface of the earth where the height of the barometer reduced to sea level is the same either at a given time or for a certain period **2** : one of two or more atoms or elements having the same atomic weights or mass numbers but different atomic numbers — **iso-bar-ic** \,ī-sə-'bär-ik, -'bar-\ *adj*
iso-bu-tyl-ene \,ī-sō-'byüt-ᵊl-,ēn\ *n* [ISV] : a gaseous butylene C_4H_8 used esp. in making butyl rubber and gasoline components
iso-chro-mat-ic \,ī-sə-krō-'mat-ik\ *adj* : ORTHOCHROMATIC
iso-chron \'ī-sə-,krän\ *or* **iso-chrone** \-,krōn\ *n* [ISV *is-* + *-chron* (fr. Gk *chronos* time)] : a line on a chart connecting points at which an event occurs simultaneously or which represents the same time or time difference
iso-chro-nal \ī-'säk-rən-ᵊl, ,ī-sə-'krōn-\ *adj* [Gk *isochronos*, fr. *is-* + *chronos* time] : uniform in time : having equal duration : recurring at regular intervals — **iso-chro-nal-ly** \'ī-ᵊl-ē\ *adv* — **iso-chro-nism** \ī-'säk-rə-,niz-əm, ,ī-sə-'krō-\ *n*
iso-chro-nous \ī-'säk-rə-nəs, ,ī-sə-'krō-\ *adj* [Gk *isochronos*] : ISOCHRONAL — **iso-chro-nous-ly** *adv*
¹iso-cli-nal \,ī-sə-'klīn-ᵊl\ *adj* [ISV] : relating to, having, or indicating equality of inclination or dip — **iso-cli-nal-ly** \-ᵊl-ē\ *adv*
²isoclinal *n* : ISOCLINIC LINE
iso-cline \'ī-sə-,klīn\ *n* : an anticline or syncline so closely folded that the rock beds of the two sides have the same dip
iso-clin-ic \,ī-sə-'klin-ik\ *adj* [ISV] : ISOCLINAL — **iso-clin-i-cal-ly** \-'klin-i-k(ə-)lē\ *adv*
isoclinic line *n* : a line on a map or chart joining points on the earth's surface at which a magnetic needle has the same inclination to the plumb line
iso-cy-a-nate \,ī-sō-'sī-ə-,nāt, -nət\ *n* [ISV] : a salt or ester of isomeric cyanic acid HNCO used esp. in plastics and adhesives
iso-cy-clic \-'sī-klik, -'sik-lik\ *adj* [ISV] : having or being a ring composed of atoms of only one element; *esp* : CARBOCYCLIC
iso-di-a-met-ric \-,dī-ə-'me-trik\ *adj* [ISV] : having equal diameters ⟨~ cells of plant parenchymatous tissue⟩
iso-dose \'ī-sə-,dōs\ *adj* [ISV] : of or relating to points or zones in a medium that receive equal doses of radiation
iso-dy-nam-ic \,ī-sō-dī-'nam-ik\ *adj* [ISV] **1** : of or relating to equality or uniformity of force **2** : connecting points at which the magnetic intensity is the same ⟨~ line⟩
iso-elec-tric \,ī-sō-i-'lek-trik\ *adj* [ISV] **1** : having or representing zero difference of electric potential **2** : being the pH at which the electrolyte will not migrate in an electrical field ⟨the ~ point of a protein⟩
iso-elec-tron-ic \-i-,lek-'trän-ik\ *adj* [ISV] : having the same number of electrons or valency electrons — **iso-elec-tron-i-cal-ly** \-i-k(ə-)lē\ *adv*
iso-en-zyme \-'en-,zīm\ *n* : ISOZYME — **iso-en-zy-mat-ic** \'ī-sō-,en-zə-'mat-ik, -zī-\ *adj* — **iso-en-zy-mic** \-en-'zī-mik\ *adj*
iso-ga-mete \,ī-sō-gə-'mēt, -'gam-,ēt\ *n* [ISV] : a gamete indistinguishable in form or size or behavior from another gamete with which it can unite to form a zygote — **iso-ga-met-ic** \-gə-'met-ik\ *adj*
isog-a-mous \ī-'säg-ə-məs\ *adj* [prob. fr. (assumed) NL *isogamus*, fr. *is-* + *-gamus* -gamous] : having or involving isogametes — compare HETEROGAMOUS — **isog-a-my** \-mē\ *n*
iso-ge-ne-ic \,ī-sō-jə-'nē-ik\ *adj* [*is-* + *-geneic* (as in *syngeneic*)] : SYNGENEIC ⟨an ~ graft⟩
iso-gen-ic \-'jen-ik\ *adj* [*is-* + *gene* + *-ic*] : characterized by essentially identical genes (identical twins are ~)
iso-gloss \'ī-sə-,gläs, -,glȯs\ *n* [ISV *is-* + Gk *glōssa* language — more at GLOSS] **1** : a boundary line between places or regions that differ in a particular linguistic feature **2** : a line on a map representing an isogloss — **iso-gloss-al** \,ī-sə-'gläs-əl, -'glȯs-əl\ *adj*
¹iso-gon-ic \,ī-sə-'gän-ik\ *or* **iso-go-nal** \ī-'säg-ən-ᵊl, ,ī-sə-'gōn-\ *adj* [ISV *is-* + Gk *gōnia* angle — more at -GON] : of, relating to, or having equal angles
²isogonic *or* **isogonal** *n* : ISOGONIC LINE
³isogonic *adj* [*isogony*, fr. *is-* + *-gony*] : exhibiting equivalent relative growth of parts such that size relations remain constant — **isog-o-ny** \ī-'säg-ə-nē\ *n*
isogonic line *n* : an imaginary line or a line on a map joining points on the earth's surface at which the magnetic declination is the same
iso-gram \'ī-sə-,gram\ *n* : a line on a map or chart along which there is a constant value (as of temperature, pressure, or rainfall)
iso-hel \'ī-sə-,hel\ *n* [*is-* + Gk *hēlios* sun — more at SOLAR] : a line drawn on a map or chart connecting places of equal duration of sunshine
iso-he-mol-y-sis \,ī-sə-hi-'mäl-ə-səs\ *n* [NL] : lysis of the red blood cells of one individual by antibodies in the serum of another of the same species
iso-hy-et \,ī-sō-'hī-ət\ *n* [ISV *is-* + Gk *hyetos* rain — more at HYET-] : a line on a map or chart connecting areas of equal rainfall — **iso-hy-et-al** \-ət-ᵊl\ *adj*
iso-la-ble \'ī-sə-lə-bəl *also* 'is-ə-\ *also* **iso-lat-able** \-,lāt-ə-bəl\ *adj* : capable of being isolated
¹iso-late \'ī-sə-,lāt *also* 'is-ə-\ *vt* **-lat-ed; -lat-ing** [back-formation fr. *isolated* set apart, fr. F *isolé*, fr. It *isolato*, fr. *isola* island, fr. L *insula*] **1** : to set apart from others; *also* : QUARANTINE **2** : to select from among others; *esp* : to separate from another substance so as to obtain pure or in a free state **3** : INSULATE — **iso-la-tor** \-,lāt-ər\ *n*
²iso-late \-lət, -,lāt\ *adj* : being alone : SOLITARY, ISOLATED ⟨standing there, ~, and still —D. H. Lawrence⟩
³iso-late \-lət, -,lat\ *n* : a product of isolating : an individual or kind obtained by selection or separation
iso-la-tion \,ī-sə-'lā-shən *also* ,is-ə-\ *n* : the action of isolating : the condition of being isolated *syn* see SOLITUDE
iso-la-tion-ism \-shə-,niz-əm\ *n* : a policy of national isolation by abstention from alliances and other international political and economic relations — **iso-la-tion-ist** \-sh(ə-)nəst\ *n or adj*
Isol-de \ī-'zōl-də\ *n* [G, fr. OF *Isolt, Iseut*] **1** : an Irish princess married to King Mark of Cornwall and loved by Tristram **2** : the daughter of the King of Brittany and wife of Tristram
iso-leu-cine \,ī-sō-'lü-,sēn\ *n* [ISV] : a crystalline essential amino acid $C_6H_{13}NO_2$ isomeric with leucine
iso-line \'ī-(,)sō-,līn\ *n* : ISOGRAM
isoln *abbr* isolation
isol-o-gous \ī-'säl-ə-gəs\ *adj* [ISV *is-* + *-logous* (as in *homologous*)] : relating to or being any of two or more compounds of related structure and a characteristic difference of composition other than CH_2 or a multiple thereof — **iso-logue** *or* **iso-log** \'ī-sə-,lȯg, -,läg\ *n*
iso-mag-net-ic \,ī-sō-mag-'net-ik\ *adj* [ISV] **1** : of or relating to points of equal magnetic intensity or of equal value of a component of such intensity **2** : connecting isomagnetic points ⟨~ line on a map⟩
iso-mer \'ī-sə-mər\ *n* [ISV, back-formation fr. *isomeric*] : a compound, radical, ion, or nuclide isomeric with one or more others
isom-er-ase \ī-'säm-ə-,rās, -,rāz\ *n* : an enzyme that catalyzes the conversion of its substrate to an isomeric form
iso-mer-ic \,ī-sə-'mer-ik\ *adj* [ISV, fr. Gk *isomerēs* equally divided, fr. *is-* + *meros* part — more at MERIT] : of, relating to, or exhibiting isomerism
isom-er-ism \ī-'säm-ə-,riz-əm\ *n* **1** : the relation of two or more compounds, radicals, or ions that contain the same numbers of atoms of the same elements but differ in structural arrangement and properties **2** : the relation of two or more nuclides with the same mass numbers and atomic numbers but different energy states and rates of radioactive decay **3** : the condition of being isomerous
isom-er-ize \ī-'säm-ə-,rīz\ *vb* **-ized; -iz-ing** *vt* : to become changed into an isomeric form ~ *vt* : to cause to isomerize — **isom-er-i-za-tion** \-,säm-ə-rə-'zā-shən\ *n*
isom-er-ous \ī-'säm-ə-rəs\ *adj* : having an equal number of parts (as ridges or markings); *esp* : having the members of each floral whorl equal in number
iso-met-ric \,ī-sə-'me-trik\ *also* **iso-met-ri-cal** \-tri-kəl\ *adj* **1** : of, relating to, or characterized by equality of measure: as **a** : of, relating to, or being an isometric drawing or projection **b** : relating to or being a crystallographic system characterized by three equal axes at right angles **2** : of, relating to, or involving isometrics — **iso-met-ri-cal-ly** \-tri-k(ə-)lē\ *adv*

APPENDIX B

McGraw-Hill Dictionary of Scientific and Technical Terms, Second Edition, 1978

ronic sequence [SPECT] A set of spectra produced by
al chemical elements ionized so that their atoms or ions
the same number of electrons.
me [BIOCHEM] Any of the electrophoretically distinct
of an enzyme, representing different polymeric states
ving the same function. Also known as isozyme.
ae [BOT] The single family assigned to the order
ics in some systems of classification.
s [BOT] A monotypic order of the class Isoetopsida
ning the single genus *Isoetes*, characterized by long,
v leaves with a spoonlike base, spirally arranged on an
ground cormlike structure.
e *See* Isoetopsida.
ida [BOT] A class of the division Lycopodiophyta;
ers are heterosporous and have a distinctive append-
e ligule, on the upper side of the leaf near the base.
nol [ORG CHEM] $C_{10}H_{12}O_2$ An oily liquid prepared
ugenol by heating, slightly soluble in water; used in the
facture of vanillin.
enol acetate *See* acetylisoeugenol.
es map [GEOL] A stratigraphic map showing the dis-
ion of one or more facies within a particular stratigraph-
t.
one [BIOCHEM] $C_{13}H_{10}O_2$ A colorless, crystalline ke-
occurring in many plants, generally in the form of a
xy derivative.
xphate [PHARM] $[(CH_3)_2CHO]_2P(O)F$ A liquid
forms hydrofluoric acid in the presence of moisture;
s a cholinergic drug in eye diseases in humans and as
tic drug in animals. Also known as DFP; diisopropyl
phosphate; diisopropyl fluorophosphonate; diisopro-
sphorofluoridate; fluostigmine; isopropyl fluophos-
e.
icandle *See* isolux.
ning [CHEM ENG] A petroleum refinery process in
olefinic naphtha is contacted with an alumina catalyst
temperature and low pressure to produce isomers of
octane number.
ata-preiso code [METEOROL] A code in which data on
s and fronts at sea level (or earth's surface) are encoded
ansmitted; a modified form of the international analysis
e.
ete [BIOL] A reproductive cell that is morphologi-
similar in both male and female and cannot be distin-
ed on form alone.
y [BIOL] Sexual reproduction by union of gametes or
iduals of similar form or structure.
eratae [BOT] A class of brown algae distinguished by
an isomorphic alternation of generations.
therm *See* geoisotherm.
o line [GEOPHYS] A line connecting points of equal
tic variation.
y [BIOL] Growth of parts at such a rate as to maintain
size differences.
[PETRO ENG] Constant gas-oil ratio.
map [PETRO ENG] Oil reservoir contour-line map that
onstant gas-oil ratios.
[GEOL] A line on a map joining those rocks compris-
ame metamorphic grade.
ent [METEOROL] A line connecting points having the
izontal gradient of atmospheric pressure, tempera-
nd so on.
[METEOROL] A line, on a given reference surface,
hrough all points where a given quantity has the same
ical value; the reference surface can be any coordinate
unctionally related to the given quantity (this includes
ly defined surfaces in space).
[ELECTR] An electronic calculator that ascertains
l and imaginary roots for algebraic equations.
] An instrument combining the functions of a
and a set square and comprising two short straight-
connected by a large circular joint with an angular-
cale.
[NAV] A line drawn on a map or chart joining points
evation.
art [NAV] A chart showing isogrivs.
[OPTICS] A dark band in an interference figure lo-
cated at those points that correspond to directions of transmission through the crystal plate in which the polarization of the incident light is not affected by passing through the plate.

Isohaline [OCEANOGR] 1. Of equal or constant salinity. 2. A line on a chart connecting all points of equal salinity.

Isoheight *See* contour line.

Isohel [METEOROL] A line drawn through geographical points having the same duration of sunshine (or other function of solar radiation) during any specified time period.

Isohemagglutinin *See* isoagglutinin.

Isohemolysin [IMMUNOL] A hemolysin produced by an individual injected with erythrocytes from another individual of the same species.

Isohemolysis [IMMUNOL] Hemolysis induced by the action of an isohemolysin.

Isohexane [ORG CHEM] C_6H_{14} A liquid mixture of isomeric hydrocarbons, flammable and explosive, insoluble in water, soluble in most organic solvents, boils at 54–61°C; used as a solvent, freezing-point depressant, and chemical intermediate.

Isohume [GEOL] A line of a map or chart connecting points of equal moisture content in a coal bed. [METEOROL] A line drawn through points of equal humidity on a given surface; an isopleth of humidity; the humidity measures used may be the relative humidity or the actual moisture content (specific humidity or mixing ratio).

Isohydric [CHEM] Referring to a set of solutions with the same hydrogen ion concentration and not affecting the conductivity of each of the various solutions on mixing.

Isohyet [METEOROL] A line drawn through geographic points recording equal amounts of precipitation for a specified period or for a particular storm.

Isohypse *See* contour line.

Isohypsic chart *See* constant-height chart.

Isohypsic surface *See* constant-height surface.

Isoimmunization [IMMUNOL] Immunization of an individual by the introduction of antigens from another individual of the same species.

Iso-Kel process [CHEM ENG] A proprietary petroleum isomerization process for the manufacture of high-octane fuel components from petroleum feedstocks.

Isokeraunic *See* isoceraunic.

Isokinetic *See* isotach.

Isokinetic sampling [ENG] Any technique for collecting airborne particulate matter in which the collector is so designed that the airstream entering it has a velocity equal to that of the air passing around and outside the collector.

Isolate [CHEM ENG] To separate two portions of a process system by means of valving or line blanks; used as safety measure during maintenance or repair, or to redirect process flows. [ELEC] To disconnect a circuit or piece of equipment from an electric supply system.

Isolated camera [ELECTR] 1. A television camera that views a particular portion of a scene of action and produces a tape which can then be used either immediately for instant replay or for video replay at a later time. 2. The technique of video replay involving such a camera.

Isolated footing [CIV ENG] A concrete slab or block under an individual load or column.

Isolated location [ADP] A location in a computer memory which is protected by some hardware device so that it cannot be addressed by a computer program and its contents cannot be accidentally altered.

Isolated point [MATH] A point p in a topological space is an isolated point of a set if p is in the set and there is a neighborhood of p which contains no other points of the set.

Isolated set [MATH] A set consisting entirely of isolated points.

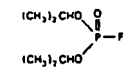
Isolating switch [ELEC] A switch intended for isolating an electric circuit from the source of power; it has no interrupting rating and is intended to be operated only after the circuit has been opened by some other means.

Isolation [CHEM] Separation of a pure chemical substance from a compound or mixture; as in distillation, precipitation, or absorption. [MED] Separation of an individual with a communicable disease from other, healthy individuals. [MICROBIO] Separation of an individual or strain from a

ISOETALES

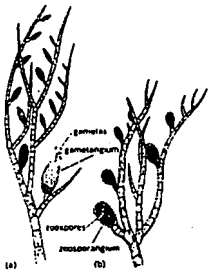
Isoetes, the entire plant. *(From A. J. Eames, in E. W. Sinnott and K. S. Wilson, Botany: Principles and Problems, 6th ed., McGraw-Hill, 1963)*

ISOFLUORPHATE



Structural formula.

ISOGENERATAE



Ectocarpus, an example of Isogeneratae showing the isomorphic alteration of generations. *(a)* Branched filament with multicellular gametangia. A gametangium is releasing biflagellate gametes. *(b)* Branched filament with unicellular zoosporangia with zoospores. *(From H. J. Fuller and O. Tippo, College Botany, rev. ed., Holt, 1954)*

natural, mixed population. [PHYSIO] Separation of a tissue, organ, system, or other part of the body for purposes of study. [PSYCH] Dissociation of a memory or thought from the emotions or feelings associated with it.

Isolation amplifier [ELECTR] An amplifier used to minimize the effects of a following circuit on the preceding circuit.

Isolation diode [ELECTR] A diode used in a circuit to allow signals to pass in only one direction.

Isolation network [ELEC] A network inserted in a circuit or transmission line to prevent interaction between circuits on each side of the insertion point.

Isolation test [ENG] A leak detection method which isolates the evacuated system from the pump, followed by observation of the rate of pressure rise.

Isolation transformer [ELEC] A transformer inserted in a system to separate one section of the system from undesired influences of other sections.

Isolator [ELECTR] A passive attenuator in which the loss in one direction is much greater than that in the opposite direction; a ferrite isolator for waveguides is an example. [ENG] Any device that absorbs vibration or noise, or prevents its transmission.

Isolead curve [ORD] A curved line, on a chart or diagram, used to show how far ahead of a moving target a weapon must be aimed to allow for the time the projectile takes to reach the target; the isolead curve connects points of equal lead on the chart or diagram.

Isolecithal *See* homolecithal.

Isoleucine [BIOCHEM] $C_6H_{13}O_2$ An essential monocarboxylic amino acid occurring in most dietary proteins.

Isolith [ELECTR] Integrated circuit of components formed on a single silicon slice, but with the various components interconnected by beam leads and with circuit parts isolated by removal of the silicon between them. [GEOL] A line on a contour-type map that denotes the aggregate thickness of a single lithology in a stratigraphic succession composed of one or more lithologies.

Isolith map [GEOL] A contour-line map depicting the thickness of an exclusive lithology.

Isolux [OPTICS] A curve or surface connecting points at which light intensity is the same. Also known as isofootcandle; isophot.

Isomagnetic [GEOPHYS] Of or pertaining to lines connecting points of equality in some magnetic element.

Isomate process [CHEM ENG] A proprietary petroleum isomerization process that takes place in the liquid phase for the manufacture of high-octane components from petroleum feedstocks.

Isomer [CHEM] One of two or more chemical substances having the same elementary percentage composition and molecular weight but differing in structure, and therefore in properties; there are many ways in which such structural differences occur; one example is provided by the compounds *n*-butane, $CH_3(CH_2)_2CH_3$, and isobutane, $CH_3CH(CH_3)_2$. [NUC PHYS] One of two or more nuclides having the same mass number and atomic number, but existing for measurable times in different quantum states with different energies and radioactive properties.

Isomerase [BIOCHEM] An enzyme that catalyzes isomerization reactions.

Isomerate process [CHEM ENG] A proprietary petroleum isomerization process that takes place in the vapor phase for the manufacture of high-octane fuel components from petroleum feedstocks.

Isomeric shift [PHYS CHEM] Shift in the Mössbauer resonance caused by the effect of the valence of the atom on the interaction of the electron density at the nucleus with the nuclear charge. Also known as chemical shift.

Isomeric transition [NUC PHYS] A radioactive transition from one nuclear isomer to another of lower energy.

Isomerism [BIOL] The condition of having two or more comparable parts made up of identical numbers of similar segments. [CHEM] The phenomenon whereby certain chemical compounds have structures that are different although the compounds possess the same elemental composition. [NUC PHYS] The occurrence of nuclear isomers.

Isomerization [CHEM] A process whereby a compound is changed into an isomer; for example, conversion of butane into isobutane.

Isomerous [BIOL] Characterized by isomerism.

Isometopidae [INV ZOO] A family of hemipteran insects in the superfamily Cimicimorpha.

Isometric *See* isochore.

Isometric drawing [GRAPHICS] A method of nonperspective pictorial drawing in which the object being drawn is turned so that three mutually perpendicular edges are equally foreshortened.

Isometric particle [VIROL] A plant virus particle that appears at first sight to be spherical when viewed in the electron microscope, but which is actually an icosahedron, possessing 20 sides.

Isometric process [THERMO] A constant-volume, frictionless thermodynamic process in which the system is confined by mechanically rigid boundaries.

Isometric projection *See* axonometric projection.

Isometric system [CRYSTAL] The crystal system in which the forms are referred to three equal, mutually perpendicular axes. Also known as cubic system.

Isometry [MATH] A mapping f from a metric space X to a metric space Y where the distance between any two points of X equals the distance between their images under f in Y.

Isomolecule *See* nonlinear molecule.

Isomorph *See* isomorphic mineral.

Isomorphic mineral [MINERAL] Any two or more crystalline mineral compounds having different chemical composition but identical structure, such as the garnet series or the feldspar group Also known as isomorph.

Isomorphism [MATH] A one to one function of an algebraic structure (for example, group, ring, module, vector space) onto another of the same type, preserving all algebraic relations; its inverse function behaves likewise. [PHYS CHEM] A condition present when an ion at high dilution is incorporated by mixed crystal formation into a precipitate, even though such formation would not be predicted on the basis of crystallographic and ionic radii; an example is coprecipitation of lead with potassium chloride. [SCI TECH] The quality or state of being identical or similar in form, shape, or structure, such as between organisms resulting from evolutionary convergence, or crystalline forms of similar composition.

Isoneph [METEOROL] A line drawn through all points on a map having the same amount of cloudiness.

Isoniazid [PHARM] $C_6H_7N_3O$ A drug used as a tuberculostatic. Also known as isonicotinic acid hydrazide.

Isonicotinic acid [ORG CHEM] $C_6H_5NO_2$ White platelets or powder, slightly soluble in water, sublimes at 260°C; used in the manufacture of isonicotinic acid hydrazide, an antitubercular agent. Also known as pyridine-4-carboxylic acid.

Isonicotinic acid hydrazide *See* isoniazid.

Isonitrosoacetophenone [ORG CHEM] $C_8H_7NO_2$ Platelike crystals with a melting point of 126–128°C; soluble in alkalies and alkali carbonates; used to detect ferrous ions and palladium. Also known as benzoylformaldoxime.

Isooctane [ORG CHEM] $(CH_3)_2CHCH_2C(CH_3)_3$ Flammable colorless liquid boiling at 99°C; slightly soluble in alcohol and ether, insoluble in water; used in motor fuels and as a chemical intermediate. Also known as 2,2,4-trimethylpentane.

Isooctyl alcohol [ORG CHEM] $C_7H_{15}CH_2OH$ Mixture of isomers from oxo-process synthesis; boils at 182–195°C; used as a chemical intermediate, resin solvent, emulsifier, and antifoaming agent.

Isopach map [GEOL] Map of the areal extent and thickness variation of a stratigraphic unit; used in geological exploration for oil and for underground structural analysis.

Isopachous line [GEOL] One of the lines drawn on a map to indicate equal thickness.

Isoparaffin [ORG CHEM] A branched-chain version of a straight-chain (normal) saturated hydrocarbon; for example, isooctane, or 2,2,4-trimethyl pentane, $(CH_3)_3C_5H_9$, is the branched-chain version of *n*-octane, $CH_3(CH_2)_6CH_3$.

Isopathic principle [PSYCH] The rule according to which a cause cures the effect, as when a feeling of guilt is relieved by an exhibition of guilt, namely hate.

APPENDIX C
Hawley's
Condensed
Chemical
Dictionary
, 17th
Edition
(2001)

catalyst. Claimed to give high yields of C_8 (xylene) isomers with low hydrogen consumption and minimal catalyst regeneration.

isoheptane. See 2-methylhexane.

isohexane. (1,2-dimethylbutane; 2-methylpentane).
CAS: 107-83-5. C_6H_{14}. A mixture of branched-chain isomers.
Properties: Colorless liquid. Boiling range 54–61C, d 0.671 (15.5/15.5C), flash p –26F (–32C) (CC).
Grade: Commercial.
Hazard: TLV: TWA 500 ppm; STEL 1000 ppm (hexane isomer). Highly flammable, dangerous fire and explosion risk, explosive limits in air 1–7%.
Use: Solvent, freezing-point depressant.

isolan. See 1-isopropyl-3-methyl-5-pyrazolyl dimethylcarbamate.

isolated double bond. Double bond separated by more than one single bond linkage from the next double bond.

isolation. Identification and separation of a pure substance that is present in trace amounts in a complex mixture. A famous instance of this was the isolation of polonium (1898) and radium (1912) from pitchblende by the Curies by coprecipitation techniques followed by repeated fractional crystallization.

isoleucine. (2-amino-3-methylpentanoic acid; Ile).
CAS: 73-32-5. $CH_3CH_2CH(CH_3)CH(NH_2)COOH$. An essential amino acid, found naturally in the L(+) form.
Properties: Crystals. Slightly soluble in water; nearly insoluble in alcohol; insoluble in ether.
Derivation: Hydrolysis of protein (zein, edestin), amination of α-bromo-β-methylvaleric acid.
Use: Medicine, nutrition, biochemical research.

"Isomate" ***[Pharmacia & Upjohn].*** TM for isocyanate foam systems. Available as nonburning, pour-in-place froth, or spray foams.

isomer. (1) One of two or more molecules having the same number and kind of atoms and hence the same molecular weight, but differing in respect to the arrangement or configuration of the atoms. Butanol (C_4H_9OH or $C_4H_{10}O$) and ethyl ether ($C_2H_5OC_2H_5$ or $C_4H_{10}O$) have the same empirical formulas but are entirely different kinds of substances; normal butanol ($CH_3CH_2CH_2CH_2OH$) and isobutanol ($[CH_3]_2CHCH_2OH$) are the same kinds of substances, differing chiefly in the shape of the molecules; *sec*-butanol ($CH_3CH_2OCH_2CH_3$) exists in two forms, one a mirror image of the other (enantiomer). Isomers often result from location of an atom or group of a compound at various positions on a benzene ring, e.g., xylene, dichlorobenzene. (2) Nuclides (i.e. kinds of atomic nuclei) having the same atomic and mass numbers, but existing in different energy states. One is always unstable with respect to the other, or both may be unstable with respect to a third. In the latter instance the energy of transformation in the two cases will differ.
See geometric isomer; optical isomer.

isomerization. A method used in petroleum refining to convert straight-chain to branched-chain hydrocarbons, or alicyclic to aromatic hydrocarbons, to increase their suitability for high-octane motor fuels. For example, butane (a gaseous paraffin hydrocarbon, $CH_3CH_2CH_2CH_3$) can be slightly modified in structure by catalytic reactions to give the isomeric isobutane ($CH_3CH_3CHCH_3$) used as a component of aviation fuel. Similarly, methylcyclopentane can be isomerized to cyclohexane, which is then dehydrogenated to benzene. Isomerization techniques were introduced on a large scale during World War II.
See isomer; chain.

α-isomethylionone. (γ-methylionone).
$C_{14}H_{22}O$.
Properties: Slightly yellow liquid. D 0.925–0.929 (25/25C), refr index 1.5000–1.5010 (20C), flash p 217F (102.7C) (TCC). Soluble in 5 parts of 70% alcohol. A synthetic product. Combustible.
Use: Floral perfumes, particularly of a violet character; flavoring.

isomorphism. The state in which two or more compounds that form crystals of similar shape have similar chemical properties and can usually be represented by analogous formulas, e.g., Ag_2S and Cu_2S.

isonipecaine hydrochloride. See meperidine hydrochoride.

isonitrile. See carbylamine.

"Isonol C100" ***[Pharmacia & Upjohn].***
$C_6H_3N[CH_2CH(CH_3)OH]_2$. An aromatic reinforcing polyol.
Properties: Amber liquid. Viscosity (50C) 1000 cP (max), d 1.055 (23C), water content 0.05%. Combustible.
Use: Ingredient of polyurethane foams, coatings, sealants, and elastomers; intermediate in organic synthesis.

isononyl alcohol. $C_8H_{17}CH_2OH$. A higher alcohol developed in early 1968. Combustible.
Use: Basis of plasticizers such as diisononyl adipate.

isooctane. (2,2,4-trimethylpentane).
CAS: 540-84-1. $(CH_3)_3CCH_2CH(CH_3)_2$.

APPENDIX D

Webster's Third New International Dictionary (Unabridged) (1971)

fr. *dissipatus* + *-lon-*, *-io* -ion] **1** : the act of dissipating or the state of being dissipated: **a** : a scattering or spreading out or being scattered or spread out to the point of destroying an original identity : DISPERSION, DIFFUSION ⟨the ~ of the enemy's forces in battle⟩ ⟨the ~ of the mist⟩ ⟨the ~ of gloom⟩ ⟨the ~ of ignorance⟩ **b** *archaic* : DISINTEGRATION, DISSOLUTION **c** : wasteful expenditure ⟨the ~ of one's energies⟩ ⟨the quick ~ of his fortune in foolish investments⟩ **d** : dissolute or intemperate living ⟨passing one's life in a round of ~⟩; *esp* : excessive drinking **2** : AMUSEMENT, DIVERSION ⟨my only ~ is an occasional Sunday concert —Havelock Ellis⟩ ⟨amidst the innumerable conflicting impulses and attractions and ~*s* of life —P.E.More⟩

dissipation of energy : a physical process (as the cooling of a body in the open air) by which energy becomes not only unavailable but irrecoverable in any form — compare CONSERVATION OF ENERGY, DEGRADATION OF ENERGY

dis·si·pa·tive \'disəˌpād·iv\ *adj* : of or relating to dissipation : tending to dissipate ⟨the loss characteristics of the ~ material —*Technical News Bull.*⟩ : marked by dissipation esp. of energy ⟨aluminum consumed in various ~ uses —D.D. Blue⟩ ⟨a ~ system⟩ — **dis·si·pa·tiv·i·ty** \ˌdisəpə'tivəd·ē\ *n* -ES

dis·si·pa·tor \'disəˌpād·ə(r), -ātə-\ *n* -S : DISSIPATER; *specif* : a part of a glacier in which the loss by melting exceeds the gain by the accumulation of snow

dissite *adj* [L *dissitus*, fr. *dis-* apart + *situs* placed — more at DIS-, SITE] *obs* : lying apart : REMOTE

disso- — see DISS-

dis·sociability \dəˌ(ˌ)di+ — *see* DISSOCIABLE\ *n.* : the quality of being dissociable or being capable of dissociation

dis·so·cia·ble \ *in sense 1* dəˈsōshəbəl *or* (ˈ)diˈs-, *in sense 2* -ōs(h)ēəb-\ *adj* [in sense 1, fr. ¹*dis-* + *sociable*; in sense 2, fr. L *dissociabilis*, fr. *dissociare* + *-abilis* -able] **1** : UNSOCIABLE **2** : capable of being dissociated : SEPARABLE

dis·social \də(s), (ˈ)di(s)+\ *adj* [¹*dis-* + *social*] : unfriendly to society : UNSOCIAL, SELFISH ⟨motivated by ~ feelings into ~ and aggressive behavior⟩

¹dis·so·ci·ant \dəˈsōs(h)ēənt\ *adj* [L *dissociant-*, *dissocians*, pres. part. of *dissociare*] : producing or resulting from dissociation; *specif, of bacteria* : MUTANT

²dissociant \ \ *n* -S : a dissociant substance or individual

¹dis·so·ciate \dəˈsōs(h)ēəˌāt, (ˈ)diˈsō-, -ōshē-, -ōs(h)ēˌāt\ *usu* |d·+V\ *adj* [L *dissociatus*, past part.] : DISSOCIATED ⟨perched on the edge of the old sofa in the living room . . . she would appear oddly ~ from her surroundings —Frances G. Patton⟩

²dis·so·ci·ate \-ōs(h)ēˌāt, *usu* -ād·+V\ *vb* -ED/-ING/-S [L *dissociatus*, past part. of *dissociare* to separate from fellowship, disunite, estrange, fr. *dis-* ¹dis- + *sociare* to join, share, fr. *socius* companion — more at SOCIAL] *vt* **1** : to cut off (as from society) : separate esp. from association or union with another : disconnect from association with another ⟨~*s* him from the company of cynics —Marya Mannes⟩ ⟨modern architecture cannot be *dissociated* from town or community planning —*Report:* (*Canadian*) *Royal Commission on Nat'l Development*⟩ ⟨*dissociated* themselves from the saloons and the distillers —M.R.Cohen⟩ ⟨never possible to ~ the meaning of words from the words themselves —Samuel Alexander⟩ **2** : to separate into discrete units or parts : DISUNITE ⟨those two elements of feeling which Freud says have become *dissociated* in the life of modern man —Irving Howe⟩ ⟨nor are Joyce's characters merely the sum of the particles into which their experience has been *dissociated* —Edmund Wilson⟩; *specif* : to subject to chemical dissociation — *vi* **1** : to undergo dissociation **2** *of bacteria* : to mutate esp. reversibly

dissociated *adj* **1** : having nothing to do with : not connected : UNRELATED ⟨inflationary rises resulting from causes ~ from money —*Current Biog.*⟩ **2** : giving evidence of or marked by psychological dissociation ⟨a ~ personality⟩ ⟨a ~ idea⟩

dis·so·ci·a·tion \dəˌsōsēˈāshən, (ˌ)diˌsō-, -ōshē- — *compare* ASSOCIATION\ *n* -S [L *dissociation-*, *dissociatio*, fr. *dissociatus* + *-lon-*, *-io* -ion] **1** : the act or process of dissociating or the state of being dissociated : SEPARATION, SEPARATENESS, DISUNION: as **a** : the process by which a chemical combination breaks up into simpler constituents usu. capable of recombining under other conditions — used esp. of the action of heat or other forms of energy on gases and of solvents upon dissolved substances ⟨~ of ammonia at high temperatures⟩ ⟨electrolytic ~⟩; compare DECOMPOSITION a, IONIZATION **b** (1) : isolation, abstraction, or extraction from the total perceptual field of some element which is to be separately observed or analyzed (2) : the separation of an idea or activity from the main stream of consciousness or of behavior esp. as a mechanism of ego defense (3) : the decompensation of defense permitting fragmentation of the ego into disunited parts (as under hypnosis or in psychotic states) **2** : the property inherent in certain biological stocks of differentiating into two or more distinct and relatively permanent strains (as the rough and smooth strains of certain bacteria); *also* : such a strain

dissociation constant *n* : a constant that depends upon the equilibrium between the dissociated and undissociated forms of a chemical combination; *esp* : IONIZATION CONSTANT — symbol *K*

dis·so·cia·tive \dəˈsōs(h)ēˌād·iv, (ˈ)diˈsō-, -ōshəd·iv, -ōs(h)ēəd·iv\ *adj* : of, relating to, or tending to produce dissociation ⟨a ~ chemical reaction⟩ ⟨the ~ phenomena associated with schizophrenia⟩; *specif* : tending to produce nonsocial or antisocial behavior ⟨~ emotions in the adolescent⟩

dis·so·conch \'disə+ˌ-\ *n* [*diss-* + *conch*] : the larval shell of a bivalve mollusk in the veliger stage

dis·sog·e·ny \dəˈsäjənē\ *also* **dis·sog·o·ny** \-ägə-\ *n* -ES [ISV *diss-* + *-geny* or *-gony*; orig. formed as G *dissogonie*] : the occurrence of sexual maturity at two distinct periods in the life of an individual (as in the larva and again in the adult of certain ctenophores)

dis·sol·u·bil·i·ty \dəˌsälyəˈbilədˑē, *archaic* disəly-\ *n* : the quality or state of being dissoluble ⟨the ~ of sugar⟩

dis·sol·u·ble \dəˈsälyəbəl, *archaic* ˈdisəly-\ *adj* [L *dissolubilis*, fr. *dissolvere* to dissolve + *-bilis* -able] : capable of being dissolved: **a** : capable of being disintegrated or decomposed ⟨matter is ~⟩ **b** : soluble in a liquid ⟨sugar is ~ in water⟩ **c** : capable of being disunited or disconnected ⟨a ~ bond between the two⟩ **d** : liable to be dispersed or terminated ⟨a ~ bank of mist⟩ ⟨a ~ contract⟩

dis·so·lute \ˈdisəˌlüt, -sələ\ *also* -səlˌyüt, *usu* |d·+V\ *adj* [L *dissolutus*, past part. of *dissolvere* to loosen, dissolve, relax, destroy — more at DISSOLVE] **1 a** *obs* : REMISS, NEGLIGENT,

APPENDIX E

The following appendix is provided as an executive summary of the technical background underlying interferences 104,771 through 104,776. It is intended to be a convenient non-technical guide for those readers who are not familiar with the technology or the discussions in the Decisions on Preliminary Motions in the respective interferences. We have tried to keep it simple by not presenting the subtleties of the art or the points of disagreement. Those familiar with the art will recognize the oversimplifications. Moreover, we have not cited the record. Detailed findings of fact are set out throughout the decisions and opinions, which stand independently of this appendix. Although we believe this summary is accurate and consistent with the findings of fact and the conclusions drawn in the decisions and opinions, it is in no way a substitute for the detailed findings of fact.

Papillomaviruses

Papillomaviruses infect a wide variety of animals, typically giving rise to growths (warts) that may be painful or unsightly, but usually not malignant. The viruses are highly species and tissue specific. For example, the virus that gives rise to plantar warts on the soles of the feet of human beings (HPV-1)

will not infect other human tissues, such as oral membranes, or any tissue of any non-human animal. By 1990, more than 50 distinct human papillomaviruses had been identified on the basis of differences among their DNA sequences, usually determined by DNA-matching ("hybridization") experiments.

Certain human papillomaviruses give rise to ano-genital warts, and certain of these viruses have been established as causative agents of cervical cancer. The type 16 human papillomavirus ("HPV-16") was the first virus implicated as a causative agent of cervical cancer. HPV-16 was identified by extracting viral DNA from an advanced cervical tumor and comparing it to the DNA of other human papillomaviruses by hybridization experiments. Because it had a low degree of hybridization (*i.e.*, did not match) with other types, it was assigned a new type number, "16." Eventually, the DNA was sequenced, and samples were distributed to numerous laboratories around the world. This first isolated and sequenced HPV-16 DNA came to be called the "prototype HPV-16" DNA. The DNA of other HPV-16s and other papillomaviruses were also isolated and used in artificial genes to make virus proteins. Several other HPV types have also been implicated as giving rise to cervical cancer.

Papillomaviruses have a protein coat or shell made of two proteins, called "L1" and "L2." The L1 protein forms the outermost shell of the papillomavirus. The exact location of the L2 protein is not known, but it is thought to be in the interior of the shell.

Virus-like particles

When viruses infect cells, the viruses take over the cellular machinery and reproduce the viral DNA and all the proteins that make up the virus. The viral coat proteins often pack spontaneously around the viral DNA to form the mature viruses. Even in the absence of the viral DNA, the viral coat proteins may aggregate to form particles having the approximate size and shape of the native virus. Such particles, if they do not contain the viral DNA, are generally referred to as "virus-like particles."

We have not been directed to any evidence of reports of recombinantly-produced virus-like particles from papillomaviruses prior to the work at issue in these interferences.

Vaccines

The immune system can protect the body against invading viruses via antibodies to the outermost coat of the virus. Any given type of antibody will bind only to a specific site having a particular molecular shape or "conformation." Antibodies that bind to specific sites, called "epitopes," on the surface of an intact virus, are said to bind to "conformational epitopes." If the antibodies bind to all the receptor sites on the virus that the virus uses to bind to cells, receptor sites will be blocked, and the ability of the virus to infect cells will be neutralized.

Antibodies are made by specialized cells. A given antibody-making cell makes antibodies that recognize only one specific epitope. When the individual is exposed to a particular virus, the cells that make the antibodies that recognize the protein coat of that virus will be stimulated to make more antibodies, and they will remember that virus. Upon future exposure to that virus, the individual's immune system will be prepared to make large quantities of those antibodies.

Vaccines work by priming the immune system to produce large numbers of neutralizing antibodies to particular viruses. In some cases, the patient can be exposed to a killed or weakened strain of the virus rather than the active virus itself. The process of killing or weakening the virus, however, may change

the exposed surface of the virus so much that few antibodies to the active virus are activated. It is also possible that the killed or weakened virus may be re-activated, leading to infection and disease rather than immunization.

A gene is a DNA molecule that carries the genetic code that instructs the cell how to make a particular protein. Genetic engineering using so-called "recombinant" techniques involves "recombining" a foreign gene with the genes of a host cell. Then the machinery of the host cell is harnessed to make the protein coded for by the foreign gene. That protein can be made in large quantities, isolated, and purified. These recombinant techniques brought hopes that the coat proteins of viruses could be produced in large quantities, cheaply, easily, and completely free of viral DNA.

If the recombinant viral coat protein had the same conformational epitopes as the proteins in the native virus, it might serve as a vaccine. Because the protein would not be subjected to the process of weakening or killing the virus, it might be more effective at priming the immune system to make antibodies against the virus than vaccines made from viruses. Moreover, a vaccine made from such proteins would carry no risk of inducing the viral disease, such as cervical cancer. Given the tendency of many viral coat proteins to form virus-like

particles, the virus-like particles, if they had the conformational epitopes of the native virus, could also serve as vaccines.

Only a couple of reports of vaccines based on recombinantly produced virus-like particles appear in the record as "prior art" to the applications involved in these interferences. The most prominent example in the record of a prior-art recombinant viral coat protein vaccine is that for hepatitis-B, which was the subject of the interference reported in *Hitzeman v. Rutter*, 243 F.3d 1345, 58 USPQ2d 1161 (Fed. Cir. 2001).

Diagnostic reagents

In addition to uses as vaccines, recombinantly produced viral coat proteins having the conformational epitopes of the L1 protein of the native virus could also be used as diagnostic reagents to determine whether an individual had been exposed to a particular type of papillomavirus. Serum from the individual would be checked for the presence of antibodies to the papillomavirus by looking for reaction with the recombinant protein. A significant degree of reaction between the recombinant protein and the serum would indicate that the serum contained an elevated level of antibodies to the papillomavirus, indicating exposure of the patient to that virus.

Proofs of the parties

In their proofs for conception and actual reduction to practice, the parties have attempted to show why their laboratory work at various stages provided sufficient evidence that various limitations of the Counts, particularly the existence of conformational epitopes, had been demonstrated. The parties mutually have challenged the sufficiency of proof each has offered for conception and actual reduction to practice of the counts in the various interferences.

In briefest outline, the positions of the parties follow.

Frazer discloses, in its Australian, PCT, and involved applications, particles made from the L1 and L2 proteins of an HPV-16 virus. These particles are significantly smaller (average diameter reported to be 35-40 nm) than all known papillomaviruses (diameters reported to be 50-60 nm). These particles are also irregularly shaped, rather than essentially spherical or icosahedral. Frazer presents no credible evidence that indicates that these particles have conformational epitopes of the native HPV-16 virus. Instead, Frazer maintains that such conformational epitopes are inherently present in the particles it produced. Frazer's position has not been accepted, and it has been denied the benefit for priority of its Australian application. (In contrast, the particles from other papillomaviruses disclosed in

Frazer's PCT application and in its involved application are about 50 nm in diameter and regularly shaped. Motions by Frazer's opponents that the disclosures of these particles failed as constructive reductions to practice of the Count were unsuccessful in the preliminary motions phase. Thus, Frazer was accorded the benefit for priority of its PCT application.)

Schlegel discloses L1 protein from HPV-1, together with experimental evidence that it maintains shows that the L1 protein has the conformational epitopes of the L1 protein in the native virion. Schlegel reports, however, that it looked for but did not find evidence indicating the presence of virus-like particles in its L1 protein preparations.

Lowy discloses virus-like particles and experimental evidence that it maintains shows that the virus-like particles it reports have at least one conformational epitope of the native virus and are capable of inducing neutralizing antibodies to the native virus.

Rose discloses virus-like particles and experimental evidence that it maintains shows that the virus-like particles it reports are conformationally correct and are recognized by antibodies from patients, including human patients, infected by the corresponding virus.

More detailed summaries of the technology and of particular technical issues involved in individual interferences may be found in the various decisions on preliminary motions and decisions on priority dates. We emphasize again that this summary is not a substitute for formal findings of fact in the decisions on priority dates.